IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	MDL No. 2:14-mn-2502-RMG
This document relates to: All Cases	

CORRECTED PLAINTIFFS' STEERING COMMITTEE MEMORANDUM OF LAW IN OPPOSITION TO PFIZER'S MOTION TO EXCLUDE PLAINTIFFS' EXPERT TESTIMONY ON THE ISSUE OF GENERAL CAUSATION

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INTRODUCTION

Although Defendant Pfizer, Inc. ("Pfizer") insists it is not so, the scientific community has reached a consensus that statins can cause diabetes. A wealth of scientific literature – including numerous epidemiological studies reported in peer-reviewed published articles – concludes that statins elevate blood glucose levels, increase the risk of new onset diabetes, and can cause diabetes. Published studies further establish that, among statins, Lipitor (also known by its generic name, atorvastatin) has an especially pronounced effect on blood glucose levels and new-onset diabetes, while certain other statins show a much smaller effect. Studies also show that this effect is most pronounced in women. One recent published study found that Lipitor can increase the risk of diabetes in women by a factor of 2.8; another published study, based on data from the Women's Health Initiative, showed a near-doubling of the risk, at a factor of 1.99. Pfizer's own clinical trials, prior to the approval of Lipitor, showed a trebling of the risk of clinically significant elevations in glucose levels in those taking the drug as compared with those taking a placebo, while in a later Pfizer study, the risk of new-onset diabetes in women increased by a factor of 2.39.

In the face of all of this evidence, Pfizer nonetheless seeks to preclude Plaintiffs, under Fed. R. Evid. 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), from introducing any expert testimony that Lipitor can cause diabetes,[1] insisting that there is no evidence to support this causal connection. Simply put, this is nonsense. Each of the studies showing that Lipitor causes diabetes relies on standard, well-accepted study designs and

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[1] Pfizer moves "to exclude expert testimony . . . that Lipitor causes diabetes, or, at a minimum, that Lipitor causes diabetes (a) at doses less than 80 mg or (b) in those with less three [out of four defined] risks factors . . . ." Pfizer Br. at 1. The argument in its memorandum, however, sweeps more broadly, attacking opinions of Plaintiffs' various experts on subjects other than causation. Because Pfizer's motion fails to give Plaintiffs or the Court proper notice of any relief it is seeking beyond the exclusion of opinions on actual causation, this Court should limit its analysis to the relief Pfizer has asked for and should consider only the admissibility of expert testimony that Lipitor causes diabetes, or that it causes it at lower doses or in the absence of risk factors specified by Pfizer.

methodologies. Plaintiffs' experts have reviewed the published, peer-reviewed scientific literature, and the underlying data, and using standard, well-accepted methodologies, including statistical techniques employed by Pfizer and its employees and consultants, offer opinions that Lipitor can cause diabetes and that women who take Lipitor are at especially high risk. Pfizer offers no genuine basis to exclude these scientific opinions. Indeed, while *Daubert* specifically cautions that the Court's gate-keeping role requires focus on principles and methodology, Pfizer's motion is targeted at a particular *conclusion*, that Lipitor can cause diabetes, not on the scientific methodology used by Plaintiffs' experts to reach this conclusion. The actual methodology that was used – analysis of randomized clinical trials, observational studies, meta-analyses, and peer-reviewed published articles, and application of the so-called "Hill Factors" to the associations found in the underlying studies – are the standard methodologies of epidemiology, the science that studies the causes of disease in human populations.

While Pfizer's motion is targeted at a particular conclusion, it pays scant attention to the actual opinions offered by Plaintiffs' experts; indeed, although it seeks to exclude the opinions of Dr. Barbara Roberts, Dr. Edwin Gale, Dr. Michael Quon, and Dr. Sonal Singh, Pfizer can scarcely be bothered to identify the opinions offered by these eminently-qualified experts, nor to point to any defects in the methodologies they used to reach their causation opinions. In this way, Pfizer avoids addressing the scientific evidence considered by these experts. And, to the extent Pfizer does address the work of these experts, it is primarily to quibble with the weight they accord to certain of the studies they considered in reaching their opinions. But this kind of second-guessing of the precise manner in which each expert carried out his or her task is beyond the scope of this Court's proper gate-keeping function.

Instead of addressing the opinions of Plaintiffs' experts who opine about causation, Pfizer engages in diversionary tactics. First and foremost, Pfizer claims that, despite a mountain of scientific evidence that Lipitor causes diabetes, it simply cannot be so because diabetes is the end-result of a gradual disease process that unfolds over a period of many years. Notably, Pfizer's argument, which finds no fault with methodology, but simply rejects the conclusion, is

not really a *Daubert* argument at all. But in any event, as discussed below, Pfizer is wrong – there is no contradiction between the existence of a gradual diabetes disease process (which Plaintiffs do not dispute) and the scientific findings that Lipitor increases the risk of, and can cause, diabetes. P

Next, Pfizer focuses its attack on two experts who do *not* offer causation opinions: Dr. Nicholas Jewell, a bio-statistician who analyzes the data from Pfizer's clinical trials, and Dr. John Abramson, a medical doctor with expertise in pharmaceutical marketing, who analyzes the discrepancy between what Pfizer's studies showed about Lipitor and diabetes and what Pfizer told doctors, patients, and regulators. Neither of these experts purports to engage in an analysis of causation; that is the work of other experts. Instead these experts note, and, in the case of Dr. Jewell, quantify, the *association* between Lipitor and diabetes shown in study after study after study. Accusing Plaintiffs' experts of conflating association and causation, Pfizer itself does precisely that, attacking as causation opinions what are clearly stated as opinions concerning the well-documented association between Lipitor and diabetes. It is true that Plaintiff' experts refer to, and build upon, each other's work (as they are permitted to do), so that Dr. Jewel's statistical analysis informs Dr. Singh's causation analysis, but it is important to note that Dr. Jewell's work is a but small part of the evidence from which Plaintiffs' other experts reach their causation opinion, and Dr. Abramson's work plays no part in those causation opinions at all. In this way, Pfizer takes aim at the wrong target, and predictably, misses the mark.

Nor are Pfizer's criticisms of Dr. Jewell's work well-taken, even on their own terms. Rather, these criticisms reflect a disagreement between Dr. Jewell and Pfizer's experts on the proper application of a common methodology. In particular, Dr. Jewell and Pfizer's experts disagree about how best to interpret the underlying data in Pfizer's clinical trials. Pfizer asks this Court to resolve this dispute and choose Pfizer's preferred interpretation. Here, too, it is beyond the scope of the *Daubert* inquiry for this Court to resolve a battle of the experts. That Pfizer's experts would have performed, or even did perform, Dr. Jewell's analyses slightly differently

provides no basis to exclude his opinions when those opinion are grounded in well-recognized statistical techniques applied with Dr. Jewell's expert judgment.

Nor do Pfizer's critiques of Dr. Jewell's work provide a basis to exclude the causation opinions of Plaintiffs' other experts. Most of Pfizer's disagreements with Dr. Jewell pertain to his analysis, in his rebuttal report of one particular Pfizer clinical trial, an analysis that Plaintiffs' other experts did not have, and did not rely on, in forming their causation opinions. And Pfizer can find no fault with the statistical analyses that Dr. Jewell performed on which Plaintiffs' experts did rely.

As demonstrated below, the opinions that Lipitor causes diabetes as offered by Drs. Gale, Quon, Singh, and Roberts are admissible under Rule 702; the related opinions concerning the association between Lipitor and diabetes offered by Drs. Jewell and Abramson are also admissible under Rule 702. Pfizer's motion should be denied in its entirety.[2]

BACKGROUND

Diabetes

Approximately 21 million people in the United States have been diagnosed with diabetes, a disease that costs Americans $176 billion in direct medical costs, with an estimated $69 billion in additional indirect costs. *See* Pfizer Ex. 11 at 1 and 8. To understand diabetes, it is necessary to understand how food is processed in the body. In order to ensure that the various tissues of the body are continuously supplied with nutrients in the amounts they need, the body needs a way of storing the energy from food after eating, and of making this available between meals. The body controls the way it stores and uses food by means of insulin. Insulin is produced in special cells known as beta cells and located in the pancreas. These can "sense" the amount of nutriment entering the blood stream from the gut, and respond by releasing insulin, which acts upon three main target tissues, the liver, muscle and fat. *See* Pfizer Ex. 11 at ¶ 6.

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[2] Pfizer states that it is moving under Fed. R. Evid. 104(a), 702, 703, and 403, *see* Pfizer Br. at 1, but it offers no arguments under Rules 104, 403, or 703. Because Pfizer has failed to support those portions of its motion, the Court should disregard them.

The body produces insulin continuously, and releases it into the blood stream in packets. The rate of insulin release is of key importance in regulating the distribution of the three main fuels (carbohydrates and the breakdown products of protein and fat) between the three main storage organs: liver, muscle, and fat. When insulin levels are high, as after a meal, the liver stores glucose instead of releasing it. Meanwhile, high levels of insulin "tell" muscle and fat to absorb and store any surplus glucose that reaches them in the circulation. Fat and protein are also stored in various ways under the control of insulin when levels are high. In between meals, insulin controls the release of circulating nutrients from their various stores. In particular, it controls the rate at which glucose is released from the liver. Pfizer Ex. 11 at ¶ 8.

The clinical definition of diabetes is persistent fasting hyperglycemia. Each year, the American Diabetes Association ("ADA") publishes current diagnostic guidelines for diabetes in a supplement to the journal DIABETES CARE. Currently, diabetes is typically diagnosed by an elevated fasting plasma glucose level of greater than 125 mg/dL[3], an HbAIC greater than 6.5%[4], and/or an oral glucose tolerance test with plasma glucose above 200 mg/dL at after two hours. Pfizer Ex. 42 at 5-6. There are many ways to get persistent fasting hyperglycemia. The most common form of diabetes is called Type 2 diabetes mellitus (T2DM), which is caused by a combination of insulin resistance and impaired insulin secretion. T2DM is often accompanied by obesity and cardiovascular complications including dyslipidemias (abnormal amount of lipids – usually in this context referring to elevated cholesterol), hypertension, accelerated atherosclerosis, coronary heart disease, stroke, and peripheral vascular disease. *Id.*

T2DM accounts for 95% of the diabetes in the U.S. and the developed world. It typically results from dysregulation of glucose homeostasis, the balance of glucose and insulin necessary

[3] Plasma glucose is the amount of glucose measured in the blood. In the United States, the unit of measurement for this is milligrams (of glucose) per deciliter (of blood), or mg/dL.

[4] HbA1c refers to glycated hemoglobin, which is a marker for and identifies the average plasma glucose level over a period of up to three months. In the United States, HbA1c has traditionally been reported as a percentage.

to maintain blood glucose. Under healthy conditions, the integrated physiology of the body seeks to maintain blood glucose at a constant level. A combination of insulin resistance and impaired insulin secretion disrupts this glucose homeostasis leading to diabetes. It is important to note that typical T2DM will not develop without both insulin resistance and impaired insulin secretion. There is a strong genetic component to predisposition to insulin resistance, impaired insulin secretion, and diabetes. However, environmental factors including lifestyle (diet and exercise) as well as other environmental factors (*e.g.*, pharmaceutical drugs like statins) play a large role in the development of new onset diabetes as well as the progression of diabetes once established. In the USA and the developed world, the rising epidemic of obesity is a major driver of insulin resistance and thus, diabetes. Lack of exercise and aging are also associated with increased insulin resistance. Women tend to be more insulin sensitive than men, although this difference is not as great after menopause. Pfizer Ex. 42 at 8.

Insulin resistance is typically defined as decreased sensitivity or responsiveness to metabolic actions of insulin. Insulin resistance plays a major pathophysiological role in T2DM and is tightly associated with major public health problems, including obesity, hypertension, coronary artery disease, dyslipidemias, and a cluster of metabolic and cardiovascular abnormalities that define the metabolic syndrome. Pfizer Ex. 42 at 8.

The natural history of T2DM typically follows a progression from development of mild insulin resistance that leads to an elevation in fasting insulin levels that is sufficient to overcome the insulin resistance and maintain normal blood glucose levels. As the body is less responsive to insulin, it manufactures more insulin to compensate for the decreased response. As obesity and aging progress and other environmental factors including statin therapy accrue, insulin resistance worsens and fasting insulin levels rise higher. After a while, in individuals with a predisposition to impaired insulin secretion, the level of insulin produced by the pancreatic cells is no longer sufficient to adequately promote glucose disposal and inhibit hepatic glucose production and thus, fasting glucose levels will begin to rise to determine a condition called glucose intolerance or prediabetes. This is often seen in the metabolic syndrome (also known as the insulin resistance

syndrome or cardiometabolic syndrome) where a clustering of insulin resistance, dyslipidemia, hypertension, and gout may exist. Pfizer Ex. 42 at 8. As the natural history unfolds with worsening insulin resistance and further impairment of insulin secretion, the fasting glucose levels or average level of glycemia (as determined by HbA1C) exceed a certain threshold and the patient may progress to frank diabetes. It is important to note that at this early stage of T2DM, the patient will have extremely elevated fasting insulin levels. But these absolute elevations in plasma insulin are insufficient to overcome the worsening insulin resistance. Thus, there is a relative rather than an absolute deficiency of insulin secretion. As the natural history of T2DM progresses, the impairment in insulin secretion will become more severe to the point where the absolute amount of insulin secreted is also deficient. Pfizer Ex. 42 at 9.

Patients in whom insulin resistance have progressed, but whose blood glucose does not reach the threshold of diabetes are said to be prediabetic. Pfizer Ex. 12 at ¶ 26. This typically involves blood glucose levels above normal – that is, above 100 mg/dL – but below the threshold for diabetes, 126 mg/dL. As the Centers for Disease Control explains:

> People with prediabetes have an increased risk of developing type 2 diabetes, heart disease, and stroke, but not everyone with prediabetes will progress to diabetes. The Diabetes Prevention Program, a large prevention study of people at high risk for diabetes, showed that lifestyle intervention that resulted in weight loss and increased physical activity in this population can prevent or delay type 2 diabetes and in some cases return blood glucose levels to within the normal range.

Pfizer Ex. 11 at 10.

People with T2DM suffer from significant morbidity and mortality with major complications in the cardiovascular system (accelerated atherosclerosis, dyslipidemias, coronary heart disease, heart failure, stroke, peripheral vascular disease leading to poor wound healing and limb amputations), as well as other major organ systems including kidney failure, fatty liver disease, autonomic neuropathy, retinopathy leading to blindness, gastrointestinal problems, etc. Pfizer Ex. 42 at 9. The major cause of death in T2DM is coronary heart disease and heart failure. If you include these cardiovascular complications, T2DM is the 5th leading cause of death in the USA. The severity of diabetes and its complications tends to increase over the natural history of

the disease because elevations in circulating glucose and lipids and an accompanying chronic inflammatory state help to worsen insulin resistance, impaired insulin secretion, and cardiovascular function in a vicious cycle. *Id.* at 9.

As noted above, a large and growing body of scientific research demonstrates that statins, including and especially Lipitor, can cause diabetes. Before turning to that body of evidence, however, it is helpful to consider the scientific method for establishing causation.

The Scientific Method for Establishing Causation

As the Supreme Court recognized in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 590 (1993), science is "a process for proposing and refining theoretical explanations about the world that are subject to further testing and refinement." It is "a way of examining the natural world and discovering important truths about it. . . . the essence of science is the scientific method." REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (3d Ed. 2011) ("RMSE") at 39.

The field of science that studies the incidence, distribution, and cause of disease is epidemiology. RMSE at 551. The first step in establishing causation is observing an association between a particular exposure and an increased risk of disease in a population. *Id.* at 552. An association between an exposure and a disease exists when they occur together more frequently than one would expect by chance. *Id.* at 566. The strength of an association can be expressed as a relative risk, an odds ratio, a hazard ratio, or an attributed risk. *Id.* Relative risk is the ratio of the incidence of the disease in those exposed to the agent to the incidence of the disease in those not exposed. RMSE at 566-68. If the relative risk is greater than 1, the risk in exposed persons is higher than the risk in non-exposed persons, suggesting a causal relationship. RMSE at 567. The extent to which the relative risk exceeds 1 reflects the strength of the association. The odds ratio compares those with the disease and those without, and measures the ratio of those with the disease who were exposed to the agent to those without the disease who were exposed. RMSE at 568-69. If the exposure is not related to the disease, the odds ratio will be 1, meaning that people without the disease were as likely to have been exposed as people with the disease. If the

exposure is positively related to the disease, the odds ratio will be greater than 1. As is true with relative risk, the higher the odds ratio, above 1, the stronger the association between the exposure and the risk. The hazard ratio is similar to the odds ratio, except that it measures the ratio at a particular point in time, rather than cumulatively. Finally, attributable risk measures the amount of disease among exposed individuals that can be attributed to the disease; it is computed by subtracting the incidence of the disease in the unexposed from the incidence in the exposed and dividing the result by the incidence in the exposed. RMSE 570-71. If the disease never occurs among the unexposed, the attributable risk will be 1, meaning that all of the disease is attributable to the exposure.

Once an association is established, scientists consider whether that association reflects an actual cause-effect relationship. *See* RMSE at 566 and 597-606. There are nine factors, often referred to as the Hill factors, that epidemiologists commonly use for this analysis, although some are more central than others, and inferences of causation do not require evidence with regard to all of the factors. RMSE at 600. These are: (1) temporal relationship; (2) strength of the association; (3) dose-response relationship; (4) replication of the findings; (5) biologic plausibility; (6) consideration of alternative explanations; (7) cessation of exposure; (8) specificity of the association; and (9) consistency with other knowledge. *See* RMSE at 601-606. After consideration of some or all of these criteria, epidemiologists may be able to make a judgment about whether there is a cause and effect relationship between an exposure and a disease. RMSE at 599-600.[5]

Associations are demonstrated through a variety of different types of scientific studies. Randomized double-blind clinical trials assign subjects at random to either an exposure group or a placebo group (or, in some comparative studies, to two different exposure groups), with neither

[5] As noted in the RMSE, "there is no threshold number that must exist" to infer causation, and the Hill factors are guidelines rather than a rigid formula or algorithm. RMSE at 599-600. As discussed below, *see infra* at I.A.2, Dr. Singh discussed and applied the Hill factors in reaching his conclusion that the association between Lipitor and diabetes is, in fact, causal.

the subject nor the investigator aware of which group the subject has been assigned. RMSE at 555. Observational studies, by contrast, compare those who have been exposed to a particular agent with those who have not. *Id.* at 556. Two important types of observational studies are cohort studies (which measure and compare the incidence of disease in the exposed and unexposed ("control") groups) and case-control studies (which measure and compare the frequency of exposure in the group with the disease (the "cases") and the group without the disease (the "controls").

Multiple studies with different conclusions, or similar conclusions of different magnitude, are frequently reviewed in a meta-analysis. "Meta-analysis is a method of pooling study results to arrive at a single figure to represent the totality of the studies reviewed. It is a way of systematizing the time-honored approach of reviewing the literature, which is characteristic of science, and placing it in a standardized framework with quantitative methods for estimating risk. In a meta-analysis, studies are given different weights in proportion to the sizes of their study populations and other characteristics." RMSE at 607.

The Strong Scientific Evidence that Lipitor Can Cause Diabetes

As one recently published article explains, "[t]he increased risk of new-onset type 2 diabetes in patients treated with statins has been well established by large meta-analyses of randomized controlled trials and observational studies." *See* Exhibit A. The abstract of a different article similarly begins by stating that "[a] wealth of evidence has established that cholesterol-lowering statin drugs, widely used for the prevention of cardiovascular disease, do increase the risk of new-onset diabetes." *See* Exhibit B. This evidence includes analyses and meta-analyses of randomized clinical trials (many conducted by Pfizer) and observational studies. These studies have compared a variety of statins to placebos, and also to each other. The evidence overwhelmingly shows that statins cause diabetes and that Lipitor is more likely to cause diabetes than many other statins.

Clinical Trials and Meta-Analyses

A large number of randomized clinical trials of various statins, including atorvastatin, has provided scientists enormous quantities of data about the relationship between statins and diabetes. These trials compare specific statins to placebo, or to each other. Significant trials run by Pfizer specific to Lipitor include:

Pfizer's NDA Submission: Pfizer's Integrated Summary of Safety, associated with its new drug application for atorvastatin, contained summaries of safety data in several pharmacological and 21 completed clinical studies, seven of which were placebo-controlled trials. Combined, these 7 studies included 1,122 participants exposed to various doses of atorvastatin, and 270 participants who received placebo. For the atorvastatin subjects, the majority received a dose of 10 mg/day (863 individuals), with the next largest group receiving 80 mg/day (94 individuals). As discussed below, a review of the data from these studies shows that, among individuals with clinically meaningful elevations in glucose levels, the average increase has been estimated to be 30.8 mg/dL. The data also show a three-fold increased incidence of clinically meaningful blood glucose abnormalities with atorvastatin as compared to placebo.

SPARCL: Pfizer's **S**troke **P**revention by **A**ggressive **R**eduction in **C**holesterol **L**evels was a double-blind, randomized, placebo-controlled multi-center trial in which patients were randomized to high-dose (80 mg) atorvastatin or placebo. SPARCL's results were published in the New England Journal of Medicine (NEJM) in August 2006, but those results did not include an analysis of any effect on glucose levels or diabetes. Pfizer Ex. 10 at 13-14; Pfizer Ex. 6 at 25. Subsequent analyses of the SPARCL data, however, show an approximate two-fold significantly increased risk of diabetes among women, with a lower increased risk among men. Pfizer Ex. 6 at 25; Pfizer Ex. 34 at 33.

ASCOT: Pfizer's Anglo-Scandinavian Cardiac Outcomes Trial ("ASCOT") trial compared two antihypertensive drugs using a prospective, randomized, open-blinded endpoint design and 10 mg atorvastatin with placebo in a double-blind randomized trial. Patients were randomized to an antihypertensive; patients with cholesterol below a specified threshold were

then eligible for randomization to either atorvastatin or placebo in the trial's Lipid-Lowering Arm ("LLA"). As a result of pre-established criteria for participation of the study, 81% of the patients in ASCOT's Lipid-Lowering Arm were male; 19% were female. In October 2002, ASCOT-LLA was stopped and unblinded. In December, 2002, after the trial was stopped, a tertiary endpoint for ASCOT's hypertensive portion was added to the lipid-lowering arm's protocol to compare the effects on the development of diabetes mellitus or renal impairment." It is not clear from the data or the published results what blood glucose level, or additional criteria, were used to define new cases of diabetes in the ASCOT trial. Dr. Jewell's analysis of the data from this trial using the standard definition for diabetes (a fasting glucose level higher than 125 mg/dL), found that, for ASCOT-LLA patients at risk for the development of new-onset diabetes, atorvastatin use was associated with a significantly increased risk of new-onset diabetes compared to placebo when controlling simply for baseline glucose, and similarly when also adjusting for three additional significant baseline predictors of new-onset diabetes in ASCOT-LLA. These analyses show a more than 30% increase in the incidence rate of new onset diabetes over an approximately three-year follow up period.[6]

These were only some of the randomized clinical trials that provide evidence that statins, and Lipitor, cause diabetes. Because of the sheer number of studies, it is not possible to consider each one here individually. But meta-analyses, typically published in peer-reviewed scientific publications, allow researchers to combine the results of a large number of clinical trials to see a summary or snapshot of the results. The chart attached as Appendix I shows the relevant meta-analyses and their results.

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[6] Two other Pfizer clinical trials, referred to as IDEAL and TNT, were analyzed by Dr. Jewell and showed increased risk of diabetes. *See* Pfizer Ex. 10 at 59-60; 80-81.

Observational Studies

In addition to the evidence from clinical trials and meta-analyses of those trials, numerous observational studies have also demonstrated the connection between Lipitor and diabetes. The following chart attached as Appendix II. Two of these studies are of particular interest. One, the Culver paper is significant because the dataset used came from the Women's Health Initiative (WHI) and thus was specific to women. Moreover, Culver's paper separated the increased risk for each of the statins, rather than combining them. The specific adjusted estimates for atorvastatin were noted to be HR 1.61. *See* Exhibit D. The second study, the Chan paper, found that statin exposure was statistically significantly associated with increased new-onset diabetes risks using multivariate analysis, with an odds ratio of 2.80 for atorvastatin. Dose response association was observed in the case of atorvastatin providing further evidence of a causal association. *See* Exhibit E.

Plaintiffs' Experts

Pfizer seeks to exclude causation opinions from six of Plaintiffs' experts (not all of whom offer opinions on causation):

Sonal Singh, M.B.B.S, M.P.H, is an Assistant Professor of Medicine in both the Division of General Internal Medicine, Department of Medicine, and in the Department of Health, Policy and Management and International Health at Johns Hopkins University. He holds a medical degree (an M.B.B.S, the Indian equivalent of an M.D.) and a Masters of Public Health. Dr. Singh is an epidemiologist and, in his current position, devotes a substantial amount of his professional time to epidemiologic research. The major focus of his research is in understanding the adverse effects of pharmacologic therapies used for chronic disease such as diabetes and atrial fibrillation. The remainder of his professional effort is dedicated to practicing general medicine and teaching activities. He teaches courses in systematic reviews, clinical epidemiology, pharmaco-epidemiology, and the practice of general internal medicine to medical students, interns, residents, and public health students at Johns Hopkins University. He also

teaches epidemiologic research methods on the topic of pharmaco-epidemiology to researchers in the Bloomberg School of Public Health at Johns Hopkins University. Pfizer Ex. 6 at 1-2.

Dr. Singh was retained specifically to offer an opinion about whether statins in general and atorvastatin in particular are causally related to the development of glucose intolerance, hyperglycemia, and type 2 diabetes, and, if so, whether the risk is higher in women than in men. Pfizer Ex. 6 at 3. In forming his opinion, Dr. Singh "employed the methods generally accepted by the scientific community and would be used to develop a peer reviewed manuscript." *Id.* at 4. These methods included his own systematic review of the published medical literature; publicly available data from the Food and Drug Administration (FDA) and Pfizer; and Dr. Jewell's analysis of the clinical trial data. Dr. Singh draws as well on his education and his own prior clinical and research experiences. Dr. Singh offers two opinions: (1) he opines that statins as a class, and atorvastatin in particular are causally linked to type 2 diabetes; (2) he opines that the risk is substantially greater in women. *See id.* at 40-41.

Michael J. Quon, M.D., Ph.D. is a Tenured Full Professor in the Department of Medicine, Division of Endocrinology, Diabetes, and Nutrition at the University of Maryland School of Medicine in Baltimore, Maryland. He also has a secondary appointment as a Full Professor in the Department of Physiology. Dr. Quon holds an M.D. and a Ph.D. in biomedical engineering. After a residency in internal medicine, Dr. Quon completed subspecialty training in Diabetes, Endocrinology and Metabolism (1990-93) at the National Institutes of Health (NIH). He has been an Investigator in the Hypertension-Endocrine Branch of the National Heart, Lung, and Blood Institute (NHLBI) at the NIH, where he established a laboratory that studied molecular mechanism of insulin action and insulin resistance as they relate to diabetes, obesity, and cardiovascular diseases. He also performed patient-oriented clinical studies to understand the physiology of glucose metabolism and the hemodynamic actions of insulin in humans. He has served as a tenured Senior Investigator and Chief of the Diabetes Unit in the National Center for Complementary and Alternative Medicine (NCCAM) at NIH where he continued laboratory and clinical studies on insulin action and insulin resistance with respect to diabetes and its

cardiovascular complications. Pfizer Ex. 42 at 1-2. As a physician-scientist at both the NIH and the University of Maryland School of Medicine, he has performed laboratory and patient-oriented clinical research on the molecular mechanisms of insulin action, diabetes, obesity, and heart disease for 25 years. He is currently the Editor-in-Chief of REVIEWS IN ENDOCRINE AND METABOLIC DISORDERS, an Associate Editor for the AMERICAN JOURNAL OF PHYSIOLOGY: ENDOCRINOLOGY AND METABOLISM, and Associate Editor for FRONTIERS IN CARDIOVASCULAR MEDICINE.

Dr. Quon provides opinions about the mechanisms of diabetes; the relationship between atorvastatin and diabetes; the studies demonstrating the association of Lipitor and diabetes; the time at which the relationship between Lipitor and diabetes was understood; the specific effect of Lipitor on diabetes in women; and the use of Lipitor for primary prevention of cardiac events in women. Dr. Quon does not specifically provide a discrete causation opinion, although he does opine on that topic; Pfizer has made no motion to exclude his opinions on any other topic.

Barbara H. Roberts, M.D. is a practicing cardiologist and a member of the clinical faculty at the Alpert Medical School of Brown University. She holds the rank of Associate Clinical Professor of Medicine and is the Director of the Women's Cardiac Center at the Miriam Hospital. The Women's Cardiac Center was a site which participated in the AIM-HIGH trial, a clinical trial comparing statin plus placebo to statin plus Niaspan in people with vascular disease and the metabolic syndrome. Dr. Roberts was a principal investigator for that study. She has authored or co-authored articles on statins in peer-reviewed journals and in the lay press. She has also lectured on lipid disorders and their treatment both in the United States and abroad. In her clinical practice, she cares for hundreds of patients with various lipid disorders, patients who have other risk factors for cardiovascular disease, and patients who have established heart disease. She has prescribed statins and other lipid-lowering drugs to patients over several decades and has extensive experience with their efficacy and their adverse effects. Pfizer Ex. 43 at 1-2.

Dr. Roberts offers four opinions: (1) Lipitor has not been shown to be effective for primary prevention in women; (2) Lipitor increases the risk of diabetes in women; (3) the consequences of diabetes are worse in women than in men; and (4) documentary evidence shows that Pfizer was in possession of information showing reasonable evidence of an association between atorvastatin and glucose dysregulation and diabetes as early as 1996. Pfizer Ex. 43 at 26. Pfizer's motion is presumably addressed to the second of these opinions.[7]

Dr. Edwin A.M. Gale, M.B., F.R.C.P is the Emeritus Chair of Diabetic Medicine at the University of Bristol, UK. From 1997-2011, he was Professor of Diabetic Medicine in Bristol, and for 5 years he was Head of the University Department of Clinical Sciences in North Bristol. He has a British medical degree and is a Fellow of the Royal College of Physicians. He has specialized in Diabetes and General Internal Medicine since 1978, and has spent approximately half of his working time since then in research and related academic activities, and about half in-patient care. He is the author of the diabetes section of Kumar and Clark, the pre-eminent British textbook of medicine, from its First through Ninth editions. He was Editor-in-Chief of DIABETOLOGIA, the journal of the European Association for the Study of Diabetes, from 2003-2010. He is a Consultant Editor for THE LANCET, and has been cited as a frequent reviewer for THE LANCET and the NEW ENGLAND JOURNAL OF MEDICINE, in addition to reviewing for many other journals. He has served on the UK MRC Cross Board Panel, which decides funding across the various areas of funding, and has also served on grant review panels for the EASD, JDRF-International and Diabetes-UK. He has advised the UK Committee for the Safety of Medicines (CSM) and its successor organization since 1999, and chaired the Special Advisory Group on Diabetes and Endocrinology to the European Medicines Agency (EMA) from 2007-2013. Pfizer Ex. 12 at 1.

[7] Dr. Roberts's first opinion, concerning the efficacy of Lipitor for primary prevention in women is the subject of a separate *Daubert* motion, *see* Docket Entry #970.

Dr. Gale offers six opinions: (1) worsening glucose tolerance is a common effect of statin therapy in general and atorvastatin in particular; (2) the effect of statins on glucose tolerance results in increased risk of progression to diabetes both in those who are prediabetic and those with normal fasting glucose levels; (3) atorvastatin increases the risk of diabetes in a sustained dose-dependent manner; (4) current evidence indicates a higher risk of statin-induced diabetes in women than in men; (5) the documented excess risk of diabetes over 5 years in some studies is of the order of 1 in 50 people treated; (6) the excess risk of progression to diabetes is inadequately conveyed in the prescribing information for physicians and the patient information sheet supplied with Lipitor. Pfizer Ex. 12 at 2.

Nicholas P. Jewell, Ph.D. has been a Professor in the Division of Biostatistics, School of Public Health, and in the Department of Statistics, both at the University of California, Berkeley, for 33 years. He holds a Ph.D. in mathematics. He is the author of a textbook, *Statistics for Epidemiology* (Chapman and Hall, New York 2003), as well as approximately 160 peer-reviewed articles in the field of biostatistics. His areas of expertise include the statistical design and analysis of studies used to investigate risk factors for disease outcomes including adverse effects, including longitudinal and survival data analysis. He is the incoming Editor for the JOURNAL OF THE AMERICAN STATISTICAL ASSOCIATION, the preeminent statistical journal in the United States. He is also a founding editor of two journals, THE INTERNATIONAL JOURNAL OF BIOSTATISTICS, and STATISTICAL APPLICATIONS IN GENETICS AND MOLECULAR BIOLOGY, and Associate Editor for the journal BIOMETRIKA. He currently serves on the Editorial Board of the Proceedings of the Royal Society B: Biological Sciences. In 2005, he received the Snedecor Award, from the Committee of Presidents of the Statistical Societies, awarded to "an individual who was instrumental in the development of statistical theory in biometry," associated with the best publication in biostatistics in the world in the previous three years. He was the 2012 recipient of the Marvin Zelen Leadership Award in Statistical Science from Harvard University. He has served as Chair of the Section on Statistics in Epidemiology of the American Statistical

Association (2009-2012). He was made a Fellow of the American Statistical Association in 1991, and a Fellow of the Institute of Mathematical Statistics in 1996. Pfizer Ex. 10 at 2.

Dr. Jewell offers three opinions in his initial report: (1) although the clinical studies submitted by Pfizer contain less than optimum information, the placebo-controlled data in those studies showed a statistically significant three-fold higher incidence of clinically meaningful abnormal increases in blood glucose measurement greater than 1.25 times the upper limit of normal, a level that, if persistent, is diagnostic for diabetes, with some evidence of a dose response; (2) analyses of the Pfizer-sponsored SPARCL trial demonstrate that there was significantly increased risk of new-onset diabetes with 80 mg atorvastatin compared to placebo and the relative risk was greater in women; and (3) analyses of two separate Pfizer-sponsored trials comparing high-dose atorvastatin therapy to low-dose atorvastatin or comparator statin therapy reveal a significantly increased incidence of new-onset diabetes with high-dose atorvastatin compared to lower-dose statin comparator; these results suggest that the effect of atorvastatin on the risk of developing new-onset diabetes differs from at least one other statin (simvastatin) and shows a dose response. Pfizer Ex. 10 at ¶¶ 6-8. Significantly, Dr. Jewell's opinions are limited to describing and quantifying the association between atorvastatin and diabetes in various clinical trials. At no point does Dr. Jewell assess whether the associations he quantifies are causal in nature.

Dr. Jewell also provided a Rebuttal Report that contains three additional conclusions: (1) For ASCOT-LLA patients at risk for the development of new-onset diabetes, atorvastatin use was associated with a significantly increased risk of new-onset diabetes compared to placebo; (2) there was no significant imbalance in Pfizer's NDA trials that would explain the disparity in levels of glucose elevation between those assigned to atorvastatin and those assigned to placebo; and (3) there is significant evidence from the SPARCL trial that atorvastatin adversely affects glucose metabolism; there was an increased risk of new-onset diabetes in SPARCL with atorvastatin whether by comparison of the incidence between the treatment groups or under a

time-to-diabetes analysis, when controlled for baseline predictors of new-onset diabetes, and in both pre-diabetics and non-pre-diabetics. *See* Pfizer Ex. 34.

John Abramson, M.D., M.Sc. is a medical doctor licensed to practice medicine in the State of Massachusetts since 1982. In addition to his M.D., he holds a Master of Science in Family Practice. The fellowship through which he earned the latter degree included the study of epidemiology, statistics, research design, and health policy, as well as training in the interpretation of scientific data. Pfizer Ex. 41 at ¶ 1. Dr. Abramson was a Senior Research Associate on the Faculty of the Institute for Health Policy, Heller School, Brandeis University from 1992 to 1993, during which he participated in a project that explored local control of healthcare resources to optimize allocation and health outcomes. He served as Chair of the Department of Family Practice at Lahey Clinic in Burlington, Massachusetts, from 1994 to 2001. He has published on health policy and the growing commercial bias in the scientific evidence that doctors rely on to guide their clinical practice. He teaches healthcare policy at Harvard Medical School. He has written about the integrity of the information that doctors rely upon when making clinical decisions. In 2002, he left clinical practice to devote himself full-time to research this topic, specifically in regard to the pharmaceutical industry and its impact on public health, public safety, and the quality of American healthcare. Since the beginning of 2002, he has been researching, writing, lecturing, and teaching about how the information about drugs and other medical products available to practicing physicians impacts their medical decisions. He has had articles published in peer-reviewed journals addressing bias in the scientific evidence upon which doctors rely.

Dr. Abramson offers 12 opinions focused on Pfizer's misrepresentations of the risk of diabetes associated with Lipitor. Pfizer Ex. 41 at 8-10. He opines about the association between Lipitor and diabetes demonstrated by particular Pfizer studies, and Pfizer's failure to provide warnings about the associations demonstrated there. He opines about the effect of drug marketing on physicians, the lack of evidence that Lipitor is effective for primary prevention in women, and the overall effect on doctors and patients of Pfizer's failure to warn about the

increased risk of diabetes associated with Lipitor, as well as Pfizer's failure to disclose that its clinical trials for Lipitor failed to demonstrate a benefit to women for use in primary prevention of heart disease. Like Dr. Jewell, Dr. Abramson does not offer an opinion that Lipitor causes diabetes. He discusses and offers opinions about the studies that demonstrate an association but he does not purport to analyze whether that association was causal. Rather, he opines that Pfizer's marketing and other representations about Lipitor failed accurately to inform doctors and patients about the association demonstrated in Pfizer's own studies.[8]

LEGAL STANDARDS

The legal standards applicable to this motion are set forth in Plaintiffs' Memorandum of Law in Response to Pfizer, Inc.'s Motion to Exclude Expert Testimony and Claims that Lipitor Is Not Effective for and Should Not Be Approved For Primary Prevention in Women and in Plaintiffs' Steering Committee Memorandum of Law in Opposition to Pfizer's Motion to Exclude Testimony of John Abramson, M.D., and Opinion Testimony Regarding Clinical Trial Data in Lipitor New Drug Application. Plaintiffs will not burden the Court with repeating them here.

ARGUMENT

I. THE TESTIMONY OF PLAINTIFFS' EXPERTS THAT LIPITOR CAN CAUSE DIABETES SHOULD NOT BE EXCLUDED

Four of Plaintiffs' experts – Dr. Sonal Singh, Dr. Michael Quon, Dr. Barbara Roberts, and Dr. Edwin Gale – have offered opinions that Lipitor increases the risk of, and causes diabetes. As discussed below, each of these doctors is highly qualified and specializes in one or more relevant areas of science and medicine. (Indeed, Pfizer does not challenge their qualifications.) Each of them has analyzed the scientific literature connecting Lipitor and diabetes, and based on this body of evidence as reflected in peer-reviewed scientific publications,

[8] Dr. Abramson's opinions are also the subject of two of Pfizer's three other *Daubert* motions, *see* Docket Entry #974 and Docket Entry #970.

has concluded that Lipitor increases the risk of diabetes and that this increased risk is greater in women than in men. Pfizer does not challenge the methodology employed by any of these experts (although it does nitpick the details of how they conducted their analyses, *see infra* at Point IA). Because these experts are qualified and because their methodologies in reaching their conclusions are unassailable (and unassailed), there is no basis to exclude their causation opinions under Rule 702 and *Daubert.*

The remaining two experts whose opinions Pfizer seeks to exclude, Dr. Jewell and Dr. Abramson, do not offer opinions that Lipitor causes diabetes. They do opine about the association between Lipitor and diabetes and, in the case of Dr. Jewell, quantify and discuss the magnitude of that association. These opinions are also fully admissible under Rule 702.

A. The Opinions of Drs. Gale, Quon, Roberts, and Singh Concerning General Causation Are Reliable, Relevant, and Admissible

Separate and apart from its attacks on the opinions of Dr. Jewell and Dr. Abramson (who do not opine about causation), Pfizer makes five arguments that Plaintiffs' general causation evidence should be excluded. As described below, none of these arguments has merit.

1. Plaintiffs' Experts Rely on the Totality of Evidence, Including Pfizer's Randomized Clinical Trials, Other Randomized Clinical Trial, Meta-Analyses, and Observational Studies

Pfizer takes Plaintiffs' experts to task for their use of particular studies in forming their opinion, but fails to recognize that each of Plaintiffs' causation experts has based his or her opinion on the totality of the evidence available – clinical trials, including but not limited to Dr. Jewell's analysis of Pfizer's own SPARCL, IDEAL, TNT, and ASCOT trials; peer-reviewed, published meta-analyses; peer-reviewed published observational studies; and, in the case of Drs. Singh, Quon, and Gale, their own scientific work. Thus, for example, Pfizer takes the experts to task for their use of the JUPITER and PROVE-IT trials, which Pfizer insists cannot establish causation. *See* Pfizer Br. at 39. But none of Plaintiffs' experts relies solely on the JUPITER trial or the PROVE-IT study; rather their opinions make clear they have considered an enormous number and variety of studies in coming to their conclusions. *See. e.g.,* Pfizer Ex. 6 at 9-23;

Pfizer Ex. 42 at 13-25; Pfizer Ex. 43 at 8-19; Pfizer Ex. 12 at 14-17. Pfizer's critiques concerning JUPITER and PROVE-IT are especially wide of the mark because: (1) neither Dr. Singh nor Gale made use of the PROVE-IT study at all; (2) although JUPITER and PROVE-IT involved statins other than atorvastatin, studies of other statins have shown that, as the FDA itself has found, the association with diabetes is a class effect, relating to the underlying mechanism of the statins themselves, for which the FDA required a class label change, *see* Pfizer Ex. 41 at ¶ 106; and (3) the FDA itself has relied the same JUPITER and PROVE-IT materials that Pfizer claims Plaintiffs' experts should have disregarded, *see* Pfizer Ex. 31; Pfizer Ex. 41 at ¶ 106.

Moreover, as epidemiologists and scientists, Drs. Singh, Quon, Roberts, and Gale are well aware of the strengths and limitations of each study they consider; their reports demonstrate as much. *See* Pfizer Ex. 6 at 4, 9-23; Pfizer Ex. 42 at 13-25; Pfizer Ex. 12 at 14-19; Pfizer Ex. 43 at 8-13. Their reports also show that they considered studies that did not entirely support their conclusions and considered alternative views and explanations, and provided a reasoned basis for why they came to the conclusions they did in light of the totality of the evidence. *Id.*[9]

Two of Pfizer's critiques warrant special attention. First, Pfizer suggests that the experts' use of Dr. Jewell's statistical analysis renders their opinions inadmissible. This is not so, for two reasons. First, as discussed below, Pfizer's criticisms of Dr. Jewell's analysis are misguided and for the most part simply wrong. *See infra* at Point IB. Because Dr. Jewell's analysis is sound and itself admissible, Plaintiffs' experts' reliance on it is no basis to exclude their opinions. But even if any of Pfizer's criticisms of Dr. Jewell were well-taken – and they are not – they would still not provide a basis to exclude the opinions of Drs. Singh, Quon, Roberts, and Gale. Many

[9] Pfizer criticizes Plaintiffs' experts for failing to consider the so-called WOSCOPS study. But Drs. Singh, Dr. Gale, and Quon all did consider WOSCOPS. *See* Pfizer Ex. 6 at 10; Pfizer Ex. 1 at ¶ 41; Pfizer Ex. 42 at 42 & Ex. B, p.5. As Dr. Gale points out, however, WOSCOPS "used a non-standard definition of diabetes, and the apparent protective effect [of pravastatin] was lost when this was reanalysed using a standard definition." Pfizer Ex. 12 at ¶ 41. WOSCOPS is particularly unhelpful here for another reason: the study included only men. *Id.*

of Pfizer's criticisms of Dr. Jewell's analysis simply do not affect the use the other experts have made of it. For example, Dr. Singh makes use of specific computations performed by Dr. Jewell with regard to the SPARCL trial, *see* Pfizer Ex. 6 at 6; whether Dr. Jewell ought to have considered other trials, or whether Dr. Jewell correctly described other aspects of his results has no bearing on the SPARCL computations that Dr. Singh used in forming his opinion. Indeed, while Dr. Singh found Dr. Jewell's individual level analysis of the SPARCL data to be the "most compelling evidence of a sex specific effect" on causation, *Pfizer does not offer a single criticism of this particular computation*. Pfizer has almost nothing to say about Dr. Jewell's analysis with respect to SPARCL at all. Thus, Dr. Singh made proper use of this concededly reliable piece of data analysis in reaching his causation opinions. The same is true for the other experts who made use of portions of Dr. Jewell's analysis that even Pfizer cannot find fault with. *See* Pfizer Ex. 12 at ¶ 49; Pfizer Ex. 42 at 17, 35; Pfizer 43 at 14.

Moreover, and significantly, Pfizer focuses much of its attack on Dr. Jewell on his analysis of the ASCOT trial in his rebuttal report. *But none of Plaintiffs' other experts relied on the Jewell rebuttal report* in forming their opinions, for the simple reason that the report was unavailable at the time they formed their opinions. Thus, even if everything Pfizer said about Dr. Jewell's analysis of ASCOT were correct (which it most assuredly is not), that analysis is simply irrelevant to the causation opinions of Drs. Singh, Quon, Gale, and Roberts. Plaintiffs' experts had other analyses of ASCOT available to them (two of the meta-analyses cited by Plaintiffs' experts – those by Sattar and the Rajapathak - included the ASCOT study, *see* Appendix I) and Dr. Singh's opinion makes clear that he relied on these published meta-analyses that included ASCOT, rather than on the analysis of ASCOT that Dr. Jewell subsequently performed.[10] Thus, ASCOT was not missing from Plaintiffs' experts' analysis, but they did not make use of Dr. Jewell's assessment of it.

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[10] Pfizer similarly argues that Dr. Jewell failed to consider the CARDS study. *See infra* at Point I.B.1.

Second, Pfizer insists that Plaintiffs' experts' use of observational studies renders their causation opinions inadmissible, because, it claims, such studies "cannot show causation." *See* Pfizer Br. at 38-41. This is simply not true. As discussed above, observational trials are a form of epidemiological experiment recognized in the Reference Manual for Scientific Evidence. They provide evidence of causation, although it is well-recognized that, standing alone, they do not provide the kind of strong evidence for causation that can be found in a randomized clinical trial. *See* RMSE at 218; *see also infra* at Point IA(4). But this makes little difference because *none of Plaintiffs' experts relies on observational trials alone in reaching an opinion of causation.* Rather, the use of these observational trials is confirmatory, providing even greater assurances that associations found in clinical trials are in fact causal. Dr. Singh, a practicing epidemiologist, addresses this very point in his Report:

> [R]andomized clinical trials are not necessary to establish causal evidence of harm since they cannot be conducted in all circumstances. There is no mechanism by which to randomly assign participants for non-modifiable exposures. The event may be sufficiently rare to be evaluated in a randomized trial. Absent such placebo-controlled trials to address this question, we rely on meta-analysis of randomized controlled trials to determine causation. Observational studies are often used in this setting.

Pfizer Ex. 6 at 5. Plaintiffs' experts properly considered the wealth of observational studies, giving them the weight they deserve and placing them in context with the clinical trials and meta-analyses to reach a judgment about causation.

Differing views about the strengths of various studies are not a basis to exclude expert testimony. *Knight v. Kirby Inland Marine Inc.*, 482 F.3d 347, 354 (5th Cir. 2007) (because, in epidemiology "hardly any study is ever conclusive," experts are not required to support their opinions with studies that "unequivocally support their conclusions"); *United States v. Bonds*, 12 F.3d 540, 561 (6th Cir. 1993) ("[a]bsolute certainty of result or unanimity of scientific opinion is not required for admissibility."); *In re Vioxx Products Liab. Litig.*, 401 F. Supp. 2d 565, 599 (E.D. La. 2005) (where both sides relied on same scientific material, but interpreted it differently and came to different conclusions, expert testimony from both sides was admissible); *Beck v.*

Koppers, Inc., No. 03-cv-60, 2006 WL 270260, *5 (N.D.Miss. Feb. 2, 2006) (failure of expert to specify weight accorded to various studies did not render ultimate judgment about the overall weight of the scientific evidence inadmissible). Pfizer clearly disagrees with the weight that Plaintiffs' experts have accorded to the various studies they considered. But that disagreement is a subject to explore on cross-examination, not a basis to exclude these qualified experts from testifying to the opinions they formed after consideration of all the scientific evidence.

2. Plaintiffs' Experts Properly Differentiate Association from Causation

Pfizer insists that Plaintiffs' experts conflate association and causation, but this is simply not so. Dr. Singh specifically addresses this issue, stating the question: "While we see that statins are associated with diabetes disease development, what circumstances can we pass from this observed association to an inference about causation?" He goes on to answer this question in a thorough analysis employing the nine Hill factors, the standard epidemiological methodology for evaluating causation. *See* Pfizer Ex. 6 at 32-39; *compare* RMSE at 599-600. He further considers alternative hypotheses and limitations. *Id.* at 39. He concludes:

> Based on the totality and weight of the evidence, including epidemiology, it is my opinion within a reasonable degree of medical and scientific certainty that statins as a class, including atorvastatin, are causally linked with type 2 diabetes. *My opinion emphasizes the causal link rather than the non-specific term association or risk and is based on a thorough review of the literature on statins and diabetes and a causality assessment and meta-analysis detailed above.*

Pfizer Ex. 6 at 40 (emphasis added).

Pfizer offers no critique of Dr. Singh's use of the Hill factors. It does not suggest, nor could it, that Dr. Singh, a medical doctor with a Masters in Public Health, lacks the expertise to make this analysis. It does not claim he used an improper methodology. Simply put, Pfizer provides no basis whatsoever to exclude the causation opinion of Dr. Singh, the primary general causation expert on whom Plaintiffs rely.[11] Moreover, Plaintiffs' other experts may rely on Dr.

[11] Pfizer does offer a number of criticisms of this opinion, claiming that Dr. Singh is "ignoring" evidence that Pfizer believes would support a different conclusion. *See, e.g.*, Points IA3, IA4, IA5. But these criticisms amount to nothing more than Pfizer's disagreement with Dr. Singh's (footnote continues on next page)

Singh's causation opinion, and may treat the association between Lipitor and diabetes as causal without the need to replicate his analysis. *See Dura Automotive Systems of Indiana v. CTS, Inc.*, 285 F.3d 609 (7th Cir. 2002); *Leese v. Lockheed Martin Corp.*, 6 F. Supp. 3d 546, 553 (D.N.J. 2014); *Ohio Envtl. Dev. Ltd. P'ship v. Envirotest Sys. Corp.*, 478 F. Supp. 2d 963, 976 (N.D. Ohio 2007).

Pfizer cites the deposition testimony of Dr. Jewell to support its claim that Plaintiffs' experts have conflated causation and association, but Dr. Jewell's deposition shows the opposite. First, as Pfizer well knows, and as Dr. Jewell confirmed at his deposition, nowhere in his expert report does Dr. Jewell use the word "cause." Dr. Jewell offers no causation opinion, for the simple reason that he was not asked to opine on this topic. Dr. Jewell's statistical analysis quantifies the association between Lipitor and diabetes, especially in women, in four of Pfizer clinical trials. Plaintiffs' other experts, including Dr. Singh, use Dr. Jewell's analysis of the data from those trials to inform their own opinions. But Plaintiffs do not offer a causation opinion from Dr. Jewell, so there was no occasion for him to address in his Report the distinction between association and causation. Second, Dr. Jewell specifically testified at his deposition that causation and association are not the same. *See* Pfizer Ex. 7 at 94:17-22. It makes no sense to say he conflated the two when he specifically stated that he did not.

Third, despite the fact that Dr. Jewell did not provide a causation opinion in his report, and does not intend to opine about causation at trial, at his deposition, Pfizer asked him whether he believed the association between Lipitor and diabetes was causal. He said that it was. Pfizer Ex. 7 at 94:5-95:7. Dr. Jewell explained that the randomization process of the clinical trials gave him sufficient comfort to treat the association as causal. *Id.* Whether or not that is methodologically sufficient is entirely beside the point, since Plaintiffs do not seek to offer that

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conclusion. In essence, Pfizer is saying: "If Dr. Singh gave those factors the weight we believe they deserve, he would not have reached the conclusion he did." But as discussed above, the weight to be accorded to any particular factor in a methodologically proper analysis is a matter for expert judgment and not grounds for exclusion under Rule 702.

opinion from him. It appears that Pfizer elicited this opinion from Dr. Jewell at his deposition for the sole purpose of excluding it. What Pfizer cannot do is use this testimony about the opinion Dr. Jewell does not intend to offer as an excuse to preclude the testimony of Plaintiffs' experts who do opine about causation.

Pfizer also cites Dr. Abramson's testimony, but takes a portion of his answer out of context to suggest a confusion that does not in fact exist. The full testimony shows that Dr. Abramson understands perfectly well the difference between association and causation, but like Dr. Jewell, also understands that in the case of a well-designed randomized clinical trial, the distinction may not be meaningful to some people:

> Q. How would you define causation and association?
>
> A. They are used interchangeably sometimes and sometimes they are used to mean that there is pathophysiological evidence that something was caused by something else as opposed to something appeared with something else.
>
> Q. How do you define it, each one of those terms?
>
> A. I think in randomized controlled trials I tend to use the word associated but other people would use the word, would say that a randomized controlled trial that's well-designed is evidence of causation.

See Pfizer Ex. 8 at 483:18-484:6; *see also id.* at 484:23-485:2 ("I think that when a clinical trial or clinical trials are well designed and there's a strong statistical signal, that one could conclude that the treatment caused the outcome.") But, as with Dr. Jewell, the issue is academic, because Dr. Abramson does not offer the opinion that Lipitor causes diabetes. *See infra* at Point IC.

3. The Risk Identified by Plaintiffs' Experts Is Neither Small nor Clinically Insignificant

Pfizer claims that Plaintiffs' experts "ignore the small size of the alleged risk," *see* Pfizer Br. at 23, but this is not so. Plaintiffs' experts quantify and discuss the magnitude of the risk. *See, e.g.,* Pfizer Ex. 6 at 9-23. The real issue is that parties *disagree* about the magnitude of the risk. The risk as identified in published scientific research, and as shown in Dr. Jewell's analysis of the data from Pfizer's clinical trials is neither small, nor, as Pfizer would have it, clinically insignificant.

As discussed above, the data in the placebo-controlled studies that were submitted as part of the NDA for Pfizer, showed a three-fold increase (3 % vs. 1 %) in the incidence of clinically significant changes in blood glucose levels in the combined Lipitor group over the incidence in the placebo group. *See* Pfizer Ex. 10 at 13. The data in Pfizer's SPARCL trial showed that Lipitor increased the risk of diabetes in women by a factor of 2.39. Pfizer Ex. 10 at 24. Two recent studies found increases in women of 2.8 and 1.99. *See* Exhibit E, Exhibit D. Together, these studies suggest that Lipitor at least doubles the risk of diabetes in women.

Pfizer argues that Lipitor increases the risk of diabetes by only 9% (an increased risk factor of 1.09), *see* Pfizer Br. at 24, but this is plainly incorrect. That figure is found in a meta-analysis published in 2010, *see* Pfizer Ex. 6 at 11, but it represents the increased risk in diabetes *for all statins*, including statins that were subsequently found to cause diabetes at far lower rates than Lipitor. The 1.09 figure also lumps together men and women; in addition, that analysis did not include data from the SPARCL trial, *see* Pfizer Ex. 29, which was specific to Lipitor. The statistics on which Plaintiffs rely, ranging from 1.99 to 2.8, are specific to women and specific to Lipitor. They are a far more accurate assessment of the risk to the plaintiff population than the number Pfizer uses.

Similarly, Pfizer dismisses the theory that Lipitor significantly raises blood glucose by claiming that the average increase in blood glucose observed in clinical trials was only 2 to 3 mg/dL. *See* Pfizer Br. at 25. Even assuming this is true, it is not the relevant statistic and does not accurately portray the magnitude of the effect of Lipitor. Averages are tricky things. The average wealth of Bill Gates and a destitute homeless person would approach $40 billion, but that is of scant comfort to the homeless person. The average increase in blood glucose across all subjects is not meaningful because Lipitor does not affect all subjects equally. If it did, then the average increase in blood glucose of those who developed new onset diabetes during a study would be the same as the average increase in those who did not develop diabetes, and one might conclude that Lipitor evenly raises blood glucose and simply nudged those closest to the threshold over the edge. Certainly that is the picture Pfizer tries to paint, but the numbers tell a

different story. What the data from Pfizer's own NDA trials shows is that for subjects who experienced clinically meaningful changes in their glucose levels, the *average* change from first measurement to last was an increase of 30 mg/dL and the *average* increase from first measurement to the highest measurement was 33.2 mg/dL. *See* Pfizer Ex. 10 at 10-13. These numbers are not trivial.[12] What they show is that, among those whom it affects, Lipitor can raise blood glucose sufficiently to take an individual with no prior glucose abnormalities – that, with a baseline glucose level less than 100 mg/dL – and elevate that individual's glucose beyond the threshold for new onset diabetes, at 125 mg/dL.

That Pfizer's experts and Plaintiffs' disagree about which is the more meaningful number, moreover, is not a basis to exclude the opinions of Plaintiffs' experts. It is the essence of expert judgment to make decisions about the relative significance of the available data. The methodology used by Plaintiffs' experts in making their calculation of the average increase they believe to be significant is basic arithmetic and standard statistical techniques, the same techniques used by Pfizer's experts. It is beyond the scope of this Court's gate-keeping function to decide which expert has exercised "better" judgment or which is more credible in explaining his or her exercise of judgment. That "battle of the experts" is for the jury to resolve. *See Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 153 (1999) (range where experts might reasonably differ, and where the jury must decide among the conflicting views of different experts).

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[12] Pfizer notes that Plaintiffs' experts testified that a .1% increase in HbA1c was not clinically meaningful or of clinical concern, *see* Pfizer Br. at 25, but this statement is both true and irrelevant. It is certainly true that a clinician would be unlikely to be concerned about an individual patient who presented with a .1% increase, but, as we have seen, the average increase across all subjects is not the point, but rather the magnitude of the effect *on those affected.* Indeed, Plaintiffs' expert Dr. Gale testified that the average across the population would translate to higher and lower numbers in individual patients and that some of those numbers would be clinically significant. *See* Pfizer Ex. 1 at 49:12-50:3; 154:1-9.

Nor do the other factors that also cause diabetes undermine Plaintiffs' causation opinions. Plaintiffs need not show that Lipitor is the sole cause of any particular plaintiffs' injury, only that it is a substantial factor. *See Ayala v. United States*, 846 F. Supp. 1431, 1441 (D. Colo. 1993), *aff'd*, 49 F.3d 607 (10th Cir. 1995) ("An act is the proximate cause of an injury if the act was a substantial factor in bringing about the injury."); *Smith v. State Comp. Ins. Fund*, 749 P.2d 462, 464 (Colo. App. 1987) (to prevail on causation, plaintiff must show that defendant's conduct was a "substantial factor" in producing the harm); *Hagen v. Celotex Corp.*, 816 S.W.2d 667, 670 (Mo. 1991) ("substantial factor" test); *Nesselrode v. Executive Beechcraft, Inc.*, 707 S.W.2d 371, 381 (Mo. 1986) ("the proximate cause of an event or injury need only be a substantial factor or efficient causal agent").[13] That there may be many causes of diabetes in no way undercuts the opinion that Lipitor is one of them.

Pfizer seeks to minimize the effect of Lipitor on diabetes by noting that other factors, such as excess weight, may have an even greater effect on the incidence of diabetes. But this is a red herring. What clinical trials measure is the number of *excess* cases of diabetes over and above the number that would be observed without Lipitor. Other risk factors and causes, no matter how substantial they may be, exist in both the placebo and Lipitor groups of the randomized clinical trials. If Lipitor doubles the risk, then *half* the women in the trial who developed diabetes while taking Lipitor would not have developed it when they did in the absence of Lipitor. Thus, it makes little difference that being overweight may have an even greater effect on the risk of diabetes in the population at large than Lipitor; randomization of the clinical trials means that overweight patients should be randomly distributed between the placebo and the Lipitor groups, so that the risk of developing diabetes from being overweight is equally

[13] This is not to say that plaintiffs need not show "but for" causation, *see Callahan v. Cardinal Glennon Hosp.*, 863 S.W.2d 852, 860 (Mo. 1993), only that, so long as "but for" causation is present, a cause need not be the sole or only cause.

present in both groups. The doubling of the risk among the randomly-assigned groups is thus the relevant statistic.

This can be easily demonstrated by imagining that, in the absence of Lipitor, one in a thousand women who are not overweight become diabetic, but among women who are overweight the rate is 250 in a thousand. This would be, of course, a 250-fold increase in the risk. Further imagine that in a randomized clinical trial of 2,000 women taking Lipitor and 2,000 taking placebo, 1,000 in each group are overweight. We would expect to see 251 cases of diabetes in the placebo group – one in the thousand who are not overweight and 250 in the 1,000 who are. If Lipitor doubles the risk of becoming diabetic, the 251 cases of diabetes among the women taking the placebo would become 502 cases of diabetes among the women taking Lipitor. If Lipitor were to treble the risk, the 251 cases would become 753! This is not a trivial or insignificant difference, even though the impact of the excess weight on the risk of developing diabetes is more than 100 times greater than the impact of Lipitor. Nor would the effect of the Lipitor be difficult to discern against the background of the effect of the weight – because randomization means that the overweight women should be evenly distributed among the two groups, it is the effect of the Lipitor, not the effect of the excess weight, that is measured in the clinical trial.

Moreover, Pfizer ignores entirely that patients with other risk factors may be at the greatest risk of diabetes and thus in the greatest need of a warning that Lipitor can increase their blood glucose and induce a condition they are already at risk for. Plaintiffs' generic causation experts, moreover, do not need to consider the relative weight of the various causes of diabetes; they opine only that Lipitor is *a* cause. As Pfizer recognizes, the relative weight of the various causes, and how they are to be evaluated in the case of any particular plaintiff, is an issue for the

parties' case-specific experts to evaluate. *See* Pfizer Br. at 24-25. It is therefore beyond the scope of this motion.[14]

4. Plaintiffs' Experts Explain the Biological Plausibility of Lipitor's Ability to Cause Diabetes

Pfizer claims that Plaintiffs' concede that biological plausibility is missing here, and that this provides a basis for exclusion. Neither is true.

To begin with, Pfizer conflates biological plausibility with the precise mechanism by which a substance causes a particular effect. The concepts are related, but they are not identical. Biological plausibility, which is one of the non-mandatory Hill factors used by epidemiologists to assess causation, asks whether a causal connection is plausible in light of other knowledge. Mechanism of action, which is not one of the Hill factors, refers to the specific mechanism by which the agent causes the effect.

In assessing whether an association demonstrated through epidemiological studies is causal, biological plausibility is a consideration, but not a requirement. On the contrary, as Dr. Hill wrote in formulating the now-canonical "Hill factors":

> It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.
>
> To quote again from my Alfred Watson Memorial Lecture (Hill 1962) there was
>
> > ". . . no biological knowledge to support (or to refute) Pott's observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th century that led to a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other 'absurd' associations, that 'it could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected.' And coming to nearer times, in the

[14] Pfizer's attempt to link the work of Plaintiffs' general causation experts to the question of case-specific causation is misguided. As the RMSE reminds, "Epidemiology is concerned with the incidence of disease in populations, and *epidemiologic studies do not address the question of the cause of an individual's disease.*" RMSE at 608.

> 20th century there was no biological knowledge to support the evidence against rubella."
>
> In short, the association we observe today may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr. Watson, "when you have eliminated the impossible, whatever remains, however improbable, must be the truth."

Austin Bradford Hill, "The Environment and Disease: Association or Causation?," Proceedings of the Royal Society of Medicine, 58 (1965), 295-300.

Consistent with Dr. Hill's insight, courts have recognized that it is not necessary for an expert offering a causation opinion based on epidemiological studies to know the precise mechanism of action. In *In re Gadolinium-Based Contrast Agents Products Liab. Litig.*, 1:08 GD 50000, 2010 WL 1796334, *5 (N.D. Ohio May 4, 2010), *mod. on other grounds*, 1:08 GD 50000, 2010 WL 5173568 (N.D. Ohio June 18, 2010), the court held: "Nothing in Rule 702, *Daubert* or the relevant case law requires experts to know the precise mechanical process underlying a cause when other evidence is sufficient to show causation." Indeed, the court further held that "[t]his is particularly true in product liability cases." *Id.., citing In re Seroquel Products Liab. Litig.*, 6:06-MD-1769-0RL-22D, 2009 WL 3806435 (M.D. Fla. June 23, 2009) (inability to identify mechanism did not render expert opinion unreliable or inadmissible); *see also Wagoner v. Exxon Mobil Corp.*, 813 F. Supp. 2d 771, 804 (E.D. La. 2011) (lack of biological plausibility goes to weight, not admissibility, of expert evidence); *In re Baycol Prod. Litig*, 532 F.Supp.2d 1029, 1066 (D.Minn.2007) ("The fact that the exact mechanism of statin-induced myopathy is not yet known does not affect the admissibility of Dr. Smith's opinion"); *Golod v. La Roche*, 964 F. Supp. 841, 858 (S.D.N.Y. 1997) ("Just as the mechanism of efficacy need not be known to support a claim that Tegison causes abatement of dermatological symptoms, so the mechanism of toxicity need not be known to support an inference of causation based on accepted clinical methods of diagnosis.");[15] *In re Phenylpropanolamine Prod. Liab.*

[15] The *Golod* case is especially instructive for its insight that a drug manufacturer need not show the precise mechanism by which a drug produces its intended effect; it is sufficient to show that it is safe and effective. 964 F. Supp. at 858. And while the effectiveness of a drug is a (footnote continues on next page)

Litig., 289 F.Supp.2d 1230, 1247 (W.D.Wash.2003); *In re Tray/sol Products Liab. Litig.*, 09-MD-01928, 2010 WL 4102247 (S.D. Fla. Sept. 10, 2010); *In re Chantix (Varenicline) Products Liab.Litig.*, 889 F. Supp. 2d 1272, 1301-02 (N.D. Ala. 2012);

Pfizer's citations are inapposite because they all deal with an entirely different scenario, where experts attempt to provide causation opinions *without* epidemiological evidence. In the absence of epidemiology, some courts have required that an expert be able to articulate a mechanism of causation. The court in *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434 (W.D. Pa. 2003) (cited by Pfizer on page 26 of its brief) made the point explicitly:

> This Court concludes that Dr. Petro's inability to show a mechanism, which is important to the Court's review of scientific reliability, demonstrates a faulty methodology that is not scientifically valid. As explained by the Federal Judicial Center, "*[i]n the absence of an understanding of the biological and pathological mechanisms by which disease develops, epidemiological evidence is the most valid type of scientific evidence of toxic causation.*" REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 126.211. Anecdotal case reports and temporal proximity do not constitute a scientifically reliable basis for Dr. Petro's opinions on general medical causation.

244 F. Supp. 2d at 572 (emphasis added). Pfizer's other citations illustrate the same principles. *See Dellinger v. Pfizer Inc.*, No. 5:03CV95, 2006 WL 2057654 (W.D.N.C. July 19, 2006) (adverse event case reports, which describe reported drug cases without comparing them to the general population or a control group, and fail to identify alternative causes or mechanism of causation provided insufficient basis for expert opinion; *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1361 (N.D. Ga. 2001) (same), *aff'd sub nom. Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194 (11th Cir. 2002); *DeGidio v. Centocor Ortho Biotech, Inc.*, 3 F. Supp. 3d 674, 687 (N.D. Ohio 2014) (same); *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1202 (10th Cir. 2002) (expert opinions excluded where experts could neither describe the mechanism involved,

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fundamentally causal inquiry – in order to obtain FDA approval, Pfizer was required to demonstrate, for example, that Lipitor *causes* a reduction in cholesterol levels – Pfizer would surely resist the notion that a drug could not be approved until the manufacturer could show not only *that* it worked but also precisely *how*.

nor cite to any studies or tests showing that the drug in question could cause high blood pressure); *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005) (where expert relied on studies of a different drug claimed to be analogous to defendant's product, inability to explain mechanism by which the other drug produced its effect rendered opinion based on analogy inadmissible.).[16]

Here, of course, Plaintiffs' experts rely on a wealth of epidemiological studies, including randomized clinical trials, meta-analyses, and observational studies. In that context, as noted, biological plausibility is a factor, but not a dispositive one. Plaintiffs' experts considered the issue of plausibility and although they agree that the specific causal mechanism has not been identified, they also agree that biologically plausible mechanisms have been identified. Thus, Dr. Singh notes that "Several studies provide evidence of plausibility." Pfizer Ex. 6 at 37. Dr. Quon discusses at length the mechanisms that have been proposed and that seem promising. Pfizer Ex. 42 at 25-29. Dr. Roberts agrees that "[t]here are several biologically plausible mechanisms which might explain the increased risk of diabetes with statins." Pfizer Ex. 43 at 17. Thus, while Plaintiffs' experts agree that the precise mechanism by which Lipitor causes diabetes has not been definitely demonstrated, they do not in any sense agree that plausibility is lacking.

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[16] Pfizer's remaining case, *Zellars v. NexTech NE., LLC*, 895 F. Supp. 2d 734 (E.D. Va. 2012), *aff'd* 533 Fed. App'x 192 (4th Cir. July 17, 2013), fits this pattern, since no epidemiological evidence was introduced, but the case is especially off-point for other reasons. In *Zellars*, the court found that the plaintiffs' expert was not qualified to offer an opinion about the toxicity of refrigerant chemicals because she had no training or expertise in either toxicology or refrigerant chemicals. To learn about these topics, she had conducted an Internet search; the results of that search "appear[ed] to be the extent of her knowledge of exposure to refrigerants." 895 F.Supp. at 747. In this context, the court noted that the proposed expert could not "describe the mechanism by which refrigerants act as neurotoxins. . . ." *Id.* Thus, the problem with the testimony in *Zellars* was not that the mechanism of action was unknown; it was that it was, apparently known to science – but not to the proposed expert.

5. The Diabetes Disease Process Does Not Undercut or Contradict Plaintiffs' Causation Opinions

Pfizer believes that Lipitor cannot cause diabetes because diabetes involves a disease process that ordinarily unfolds over a period of many years.[17] Pfizer attempts to couch this argument as an attack on the methodology of Plaintiffs' experts by claiming that, because Plaintiffs' experts disagree with Pfizer's conclusion, they must be "ignoring" this fundamental fact about diabetes. Of course, to suggest that highly-credentialed experienced doctors whose entire careers have been devoted to the study of diabetes have simply forgotten about, or ignored, the most fundamental facts about the disease is ludicrous. These doctors are well aware that diabetes is a disease process that unfolds over time. Indeed, Drs. Quon and Gale devote substantial portions of their reports to this process. *See* Pfizer Ex. 42 at 23-25; Pfizer Ex. 12 at 17-19. Plainly, they have neither overlooked nor forgotten it in rendering their opinions. Dr. Singh, moreover, explicitly states that "[t]he cause and effect relationship between statins and diabetes is consistent with our knowledge of the natural history and biology of diabetes." Pfizer Ex. 6 at 38. Pfizer's argument should be rejected because the opinions of these experts demonstrate that there is no contradiction between the diabetes disease process and the conclusion that Lipitor causes diabetes, for at least three reasons.

First, that a disease process may be underway does not ensure that it will ever develop into full-blown disease, nor does it determine the point at which that will occur. *See* CDC National Diabetes Report ("not everyone with prediabetes will progress to diabetes"). In that context, Lipitor can make the difference between a disease process that never turns into diabetes and a case of new onset diabetes, or between a case of diabetes now instead of ten years from now. Dr. Quon, who describes the diabetes disease process in details, explains:

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[17] More accurately, Pfizer's lawyers believe this, for nowhere does Pfizer claim that its own experts perceive a contradiction between the diabetes disease process and the possibility that Lipitor causes diabetes. This argument thus appears to be a made-for-litigation argument without even the veneer of scientific basis.

> Any drug that promotes insulin resistance or glucose intolerance in humans is predicted to increase the incidence of new onset diabetes. This is because the two major pathophysiological abnormalities in type 2 diabetes are insulin resistance and impaired insulin secretion. In any population with a fixed percentage of people with impaired insulin secretion and beta cell function, increasing the incidence or severity of insulin resistance or glucose intolerance (a combination of insulin resistance and impaired insulin secretion) will necessarily result in more people with a diagnosis of frank diabetes. Atorvastatin therapy unequivocally increases insulin resistance and/or glucose intolerance in a dose-dependent manner.

Pfizer Ex. 42 at 20. Thus, Lipitor can *accelerate* an existing diabetes disease process. As noted above, Plaintiffs need not show that Lipitor was the sole or "original" cause of any particular plaintiffs' diabetes, only that it was a substantial factor. *See, e.g., Ayala*, 846 F. Supp. at 1441; *Smith*, 749 P.2d at 464; *Hagen*, 816 S.W.2d at 670; *Nesselrode*, 707 S.W.2d at 381. Thus, Lipitor can cause diabetes, in both the real and the legal sense, even in a plaintiff in whom the diabetes disease process had already commenced.

Moreover, the causal inquiry includes the question *when* the plaintiff would have developed diabetes, for even those who may eventually have progressed to diabetes would not have become diabetic as soon as they did. This is significant because the damage to the body caused by diabetes is both significant and progressive; the sooner one crosses to full-blown diabetes, the more damage one will suffer from it as a result. Even if it were true that Lipitor only causes diabetes in those destined to get it anyway (which it is not), the *reductio absurdum* of Pfizer's disease process argument would be to say that a toxic substance that outright kills does not "cause" death, since the person was certain to die eventually in any event. Pfizer's argument is different only in degree and is no more valid.

Plaintiffs note, as well, that for those in whom the disease process was already underway, the failure to warn about the increased risk of diabetes, and the failure to instruct doctors to monitor blood glucose levels, was especially pernicious, as it is precisely these individuals in whom Lipitor should not have been prescribed, or should have been prescribed with caution, and, in any event, whose blood glucose levels were most in need of monitoring.

Pfizer's disease-process argument fails for a second reason: It is not the case that Lipitor causes diabetes only in those in whom the diabetes disease process is already underway, or at least not to the extent detectable. Even individuals with low or normal glucose developed diabetes at a greater rate while taking Lipitor as compared to those taking a placebo. Indeed, Dr. Gale expressly considered the question whether Lipitor only induces diabetes in those already like to develop it. As he explains, "the point at issue is not whether those closest to a diagnosis of diabetes will be the first to develop the condition when exposed to a diabetogenic agent; this is to be expected. The real point is whether statin therapy promotes progression to diabetes once these risk factors have been corrected for." Pfizer Ex. 12 at ¶ 53. Considering the epidemiological evidence, Dr. Gale concludes that "the risk of diabetes on statin therapy is increased across the board, and *not merely in those with pre-existing risk factors for diabetes*." *Id.* (Emphasis added.) Thus, although diabetes may involve a long, slow process, statin therapy can induce diabetes even in those in whom this process has either not begun or is not well-developed. In this respect, it is significant that, as discussed below, the average amount by which Lipitor was found to elevate blood glucose levels in individuals in whom clinically-significant glucose abnormalities were noted during the placebo-controlled trials in Pfizer's Lipitor NDA trial was 30 mg/dL. *See infra* at Point II. This amount is sufficient to raise blood glucose levels from normal (less than 100) all the way to diabetic (more than 126) during the course of statin therapy. Apparently, Lipitor can not only accelerate the disease process, it can create a shortcut for it.

Third, Pfizer's argument fails because Lipitor-induced diabetes may itself take years to develop. One review of Pfizer's clinical trial data showed that the gap between the risk of diabetes in those taking Lipitor and those taking placebo increased over time, becoming more pronounced as the years of statin therapy went by. *See* Exhibit F. So although Lipitor can cause diabetes in relatively short periods of time, as evidenced by Pfizer's relatively short early clinical trials, its effect appears to be more pronounced after longer exposure. Even a slow disease process may be induced (as well as accelerated) by Lipitor.

B. **Dr. Jewell's Statistical Analysis Is Reliable, Relevant, and Admissible**

Dr. Jewell does not offer an opinion that Lipitor causes diabetes. He does however provide important statistical analysis on which Plaintiffs' other experts rely, in part, for their causation opinions. Pfizer has not moved to exclude Dr. Jewell's statistical analysis, nor his opinions about the association between Lipitor and diabetes. Rather, it seeks only to exclude his "causation" opinions – of which there are none. Nonetheless, because Pfizer devotes a substantial portion of its brief to Dr. Jewell's analysis, and because Plaintiffs' other experts make use of Dr. Jewell's statistical analysis, Plaintiffs here respond to those arguments.

Dr. Jewell's original report analyzed the data from four of Pfizer's clinical trials for Lipitor: (1) the pooled placebo-controlled clinical trials submitted by Pfizer to the FDA with the NDA for Lipitor; (2) the SPARCL trial; (3) the TNT trial; and (4) the IDEAL trial. These data derived from was a randomized, controlled clinical trials conducted by Pfizer. Using standard statistical methodologies, Dr. Jewell analyzed the data from these trials to determine the extent to which they showed an association between Lipitor and diabetes or clinically meaningful glucose elevations. In his rebuttal report, Dr. Jewell analyzed the data from a fifth Pfizer randomized clinical trial, the ASCOT-LLA trial.

In some instances, Dr. Jewell's conclusions are different from those drawn by Pfizer's experts, or by Pfizer at the time of the various clinical trials. Although there is no dispute about the numbers themselves, there is some disagreement about which data are most significant for purposes of this analysis. That the parties disagree about the significance of the data is hardly surprising in an undertaking that calls for the exercise of expert judgment. Dr. Jewell, of course, is a renowned expert in precisely this kind of bio-statistical analysis. He has exercised his professional judgment in analyzing the data Pfizer gathered in its trials. Pfizer suggests that it was somehow improper for Dr. Jewell to perform his own analysis, that he was somehow required to accept the analysis of Pfizer and its experts. This is nonsense. Because Dr. Jewell himself possesses the requisite expertise and experience to perform the statistical analysis of the

data Pfizer gathered, his analysis is fully admissible, so long as the methodologies he used to conduct that analysis do not render his conclusions unreliable.

Pfizer claims to discern several methodological flaws in Dr. Jewell's analysis, but these are not in fact defects in the *methods* used by Dr. Jewell. They are primarily disagreements about Dr. Jewell's judgments in applying standardized methodologies or, in one instance, an inaccuracy in the way Dr. Jewell described one of his results, which even Pfizer concedes does not affect any of his actual statistical computations. None of them call into question the reliability or admissibility of Dr. Jewell's statistical opinions.

1. Dr. Jewell's Methodology Is Identical to That Used in Numerous Peer-Reviewed, Published Articles

Pfizer takes Dr. Jewell to task for not including ASCOT and an additional Pfizer study, the so-called CARDS study, in his initial analysis; Pfizer contends that the selection of the studies to analyze amounts to "cherry-picking." But Dr. Jewell did not select the studies to analyze; rather he chose to follow the analysis performed by Dr. Waters and others in a meta-analysis published in 2011. *See* Pfizer Ex. 29. In that paper, Dr. Waters and his team analyzed three Pfizer clinical trials – the SPARCL, TNT, and IDEAL studies – to assess the extent of the association between Lipitor and diabetes.[18] Dr. Waters has been a Pfizer consultant since 2004; between 2004 and 2014, Pfizer paid him more than $1.7 million. *See* Exhibit G. Three of the other authors of the Waters paper are identified in the paper as Pfizer employees. *See* Pfizer Ex. 29. Dr. Jewell analyzed precisely the same three studies that Dr. Waters did, SPARCL, TNT, and IDEAL, and threw in data from the placebo-controlled clinical trials in Pfizer's own Lipitor NDA trials as well. If these were the "wrong" studies, they were the wrong studies for Dr. Waters to analyze, too. Thus, while Pfizer contends that Dr. Jewell himself selected these

[18] Dr. Waters apparently selected these three studies because they were not included in the meta-analysis published by Sattar *et al.* *See* Pfizer Ex. 29 at 1536. The Sattar analysis *did* include the ASCOT trial, which Pfizer claims Dr. Jewell should have considered; presumably its inclusion there explains why Dr. Waters did not include it in his article. *See* Exhibit H at 737.

studies in order reach a pre-ordained result, the evidence shows that Dr. Jewell simply adopted Dr. Waters's selection. If this was cherry-picking, it was Pfizer that picked the cherries.[19]

But Pfizer's "wrong studies" argument fails for two other, more significant reasons. First, none of Plaintiffs' causation experts relied solely on the studies that Dr. Jewell analyzed. Rather, as clearly set forth in the reports of Drs. Singh, Quon, Gale, and Roberts, Plaintiffs' causation experts looked at a vast amount of research concerning statins in general, and Lipitor in particular before determining that Lipitor causes diabetes. Dr. Jewell's selection did not limit the work of the other experts. Indeed, certain of the meta-analyses that Dr. Singh considered included the ASCOT trial in their analysis. *See* Pfizer Ex. 6 at 11, 14-15. Dr. Roberts also considered both the ASCOT study and the CARDS study in her report *See* Pfizer Ex. 43 at 4, 7. Thus, Pfizer's contention that any causation opinion in this case is based solely on an analysis of the SPARCL trial, *see* Pfizer Br. at 35, is simply false.

Second, Dr. Jewell did in fact analyze one of the two studies Pfizer says he ought to have looked at, the ASCOT study, in his rebuttal report. (His findings there are discussed below, *see infra* at Point IB3.) The other study Pfizer believes Dr. Jewell should have considered, the CARDS study, was a study of the effect of Lipitor in patients who already had diabetes. CARDS may or may not provide evidence concerning the efficacy of Lipitor for primary prevention in women, the fact that all of the study subjects already had diabetes precludes its use in determining whether Lipitor can cause new onset diabetes. So of the two studies Pfizer claims Dr. Jewell ignored, ASCOT and CARDS, he in fact analyzed one of them and the other was irrelevant to the issue here. Moreover, as discussed above, because Dr. Jewell formed no

[19] The Court may take note that even the Waters study suggested that the "potential increased risk of new-onset [Type 2 diabetes] with atorvastatin might warrant careful monitoring." *See* Pfizer Ex. 29. Pfizer, of course, prevented practicing physicians, including Plaintiffs' doctors, from engaging in that "careful monitoring" or from forming their own clinical judgment about the relative strengths of the risks and benefits of Lipitor because it concealed the causal link between Lipitor and diabetes in women and failed to provide adequate warnings about the effects of Lipitor on blood glucose and the need for glucose monitoring in patients taking Lipitor.

causation opinion, it makes little sense to take him to task for the studies he did not analyze. Dr. Jewell's assignment was to drill into the data underlying the NDA, as well as the SPARCL, TNT, and IDEAL studies, not to weigh the totality of the evidence concerning Lipitor and diabetes.

Pfizer also takes Dr. Jewell to task for analyzing studies with respect to end-points that were not pre-specified in the study. But here, too, Pfizer ignores that *Dr. Jewell's methodology is identical to that used by Dr. Waters*. As noted, the Waters paper analyzed the same studies and also reached conclusions about the association between Lipitor and diabetes. The JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, which published the paper, apparently had no quarrel with Dr. Waters's methodology and saw no problem with the use of these studies. The Waters paper is not the only example of peer-reviewed, published scientific articles analyzing studies with respect to end-points that were not pre-specified. The Waters article responds to an article by Sattar and colleagues, which analyzed the effect of statins on new-onset diabetes in 13 clinical trials. As described in the Sattar article, the studies the scientists looked at "were designed to assess the effect of statin treatment on cardiovascular endpoints in stable individuals." Exhibit H. That is, they were not designed to assess the increased risk of diabetes. Nonetheless, that is precisely what Sattar used them for, in concluding that statin therapy is associated with an increased risk of diabetes. The prestigious British medical journal, THE LANCET, published the article, again apparently without quarrel about the methodology. The same is true for the meta-analyses published by Rajapathak, Coleman, Preiss, Navarese, Goodarzi in publications such as the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA), and the AMERICAN JOURNAL OF CARDIOLOGY. Dr. Jewell's analysis thus follows a methodology used by practicing scientists in the field that has been subjected to peer-reviewed publication.

Moreover, as Pfizer well knows, randomized clinical trials with diabetes as a pre-specified endpoint do not exist.[20] But Dr. Singh, an epidemiologist with years of specific experience and expertise in this precise area, explains that such studies, while desirable, are not necessary in the formation of an opinion about causation:

> The definitive randomized controlled trial in which patients would be randomized to statins and/or placebo and measure the outcome of diabetes would be ideal. However, such a randomized trial does not exist. To my knowledge, there are no randomized clinical trials wherein subjects were randomly assigned to statins vs. controls, and where diabetes was the pre-specified outcome of interest, but diabetes has been collected as an adverse event in trials of statin therapy. Such a definitive randomized trial would be considered unethical according to a report by the Institute of Medicine on post-marketing safety studies if the weight of evidence suggested that statins may have a role in the development of diabetes.
>
> Short of a definitive randomized clinical trial data on the outcome of interest, causal inference must be drawn from robust meta-analysis of randomized controlled trials or observational studies.

Pfizer Ex. 6 at 5. It would appear the scientific journals that published the articles discussed above agree.

Finally, Pfizer distorts beyond recognition the meaning of *Daubert* when it contends that Dr. Jewell's results are unreliable within the meaning of Rule 702 because they are made for litigation and they have not been published, *see* Pfizer Br. at 35. Of course, Dr. Jewell was only given access to the data because of this litigation, and is precluded by the confidentiality strictures that accompanied Pfizer's production of data in this litigation from publishing his results. Nothing in the *Daubert* opinion, bhowevr, suggests that publication of the results and opinions specific to a litigation is a criterion or even a consideration under *Daubert.* The issue is whether the *methodology* has been the subject of peer-reviewed publication. *See Daubert*, 509 U.S. at 593 ("Another pertinent consideration is whether *the theory or technique* has been subjected to peer review and publication") (emphasis added). Nor is it surprising that a retained

[20] Pfizer claims that ASCOT fits into this category, but, as discussed below, this was not actually the case. *See infra* Point I.B.3.

expert offers an opinion he formed for the litigation. The issue is whether the methods Pfizer can find no fault with the statistical techniques used by Dr. Jewell to analyze precisely the same studies selected by its own consultant.

2. Dr. Jewells' Definition of "Glucose Abnormalities" Does Not Render Any of His Opinions Unreliable

Pfizer makes much of an error in Dr. Jewell's report that even Pfizer admits had no effect on the statistical calculations Dr. Jewell performed with respect to the association of Lipitor and diabetes. Nor did this error have any effect on the use Plaintiffs' other experts have made of Dr. Jewell's analysis. Nonetheless, Pfizer seeks to use this irrelevant error as a basis to exclude Dr. Jewell's statistical opinions.

Dr. Jewell correctly analyzed cases the increased risk of diabetes in the NDA trials and the increased risk of new onset diabetes in the SPARCL, TNT, IDEAL, and ASCOT trials. He used the ADA diagnostic criteria for diabetes, a blood glucose level above 125, and included all study participants who did not have a diagnosis of diabetes and whose baseline blood glucose did not put them over the diabetes threshold — the very same inclusion criteria Dr. Waters used.. In discussing the results of his analysis, Dr. Jewell erroneously characterized all of the new cases of diabetes as occurring in subjects "without baseline glucose abnormalities." *See* Pfizer Ex. 10 at 7 & n.1; *see also id.* at 43-47. In fact, *some* of the cases of new onset diabetes involved subjects with baseline blood glucose levels between 100 mg/dL and 125 mg/dL, which is to say, these subject had abnormal blood glucose and were in the category generally considered to be pre-diabetic. Dr. Jewell thus incorrectly characterized some of the patients with new onset diabetes as having been without glucose abnormalities at baseline. He did so in the context of discussing the benefits of statins that such patients could derive, not in the context of discussing the association between Lipitor and diabetes. *See* Pfizer Ex. 10 at 7. While it is true that Dr. Jewell's original analysis did not differentiate between those who went from normal blood glucose levels to diabetic levels, on the one hand, and those who went from abnormal, prediabetic glucose levels to diabetic levels, on the other, such differentiation is entirely separate

from the larger question of causation. As other researchers have done, Dr. Jewell correctly included these prediabetic patients in his analyses, since prediabetic patients are at risk for developing diabetes.

Pfizer grudgingly admits that Dr. Jewell's mischaracterization of some of the patients' baseline glucose status did not impair his statistical analysis in any way. *See* Pfizer Br. at 27. It nonetheless insists that this non-statistical, non-computational error provides a basis to exclude Dr. Jewell's statistical opinions. It does not. Specifically, Dr. Jewell's terminology had no effect on his conclusion that

> There was a statistically significantly increased Relative Risk of new-onset diabetes in the SPARCL data with atorvastatin use whether defined by adverse event reporting or through post-baseline glucose values. It persisted when controlling for baseline glucose value and a history of Diabetes Mellitus, and the effect was greater in women. Patients without baseline diabetes or hyperglycemia who were treated with atorvastatin were at a 60% increased risk for the development of NOD according to either definition.

Pfizer Ex. 10 at ¶ 52. Nor did it have any effect on his computation that in women, the increased relative risk for new onset diabetes was 2.4. *Id.* at 24-25. Yet these are the conclusions on which Plaintiffs' other experts relied in forming their causation opinions. *See* Pfizer Ex. 6 at 25 ("Dr. Jewell's analysis of Pfizer's Summary of Clinical Safety for SPARCL noted "a greater incidence of the reported adverse event of diabetes mellitus (preferred term) in the atorvastatin than placebo group"); *id.* at 29 ("The most compelling evidence of a sex specific effect comes from the individual level analysis of the SPARCL data above. The analysis clearly indicates that the risk of diabetes among women taking atorvastatin is approximately two-fold compared to placebo."); Pfizer Ex. 42 at 17-18 (noting Dr. Jewell's analysis of SPARCL trial showing relative risk of developing diabetes for women on atorvastatin was 2.39); Pfizer Ex. 43 at 14 (discussing both Waters and Jewell analysis of SPARCL); Pfizer Ex. 12 at ¶ 50 (noting, among other data from other studies, relative risk for women in SPARCL as computed by Jewell to be 2.39 and stating "[t]hese data indicate that an enhanced risk in women does appear more likely than not, to a reasonable degree of scientific certainty").

Nor do any of the opinions offered by Plaintiffs' other experts use Dr. Jewell's terminology to differentiate causation specifically in individuals without previous glucose abnormalities. Dr. Gale does opine that "the effect of statins on glucose tolerance results in increased risk of progression to diabetes both in those who are prediabetic and those with normal fasting glucose levels," but Dr. Gale's report makes clear that he is using 100 mg/dL as the cutoff for prediabetes and 126 mg/dL as the cutoff for diabetes, exactly as Pfizer contends should be done. *See* Pfizer Ex. 12 at 7-8. Dr. Singh does not offer an opinion relating to whether the cases of new-onset diabetes observed in the various studies had previous glucose abnormalities. *See* Pfizer Ex. 6 at 40-41. The only causation opinion that Dr. Roberts offers is that "Lipitor clearly increases the risk of developing diabetes in women." Pfizer Ex. 43 at 26. This opinion clearly not does not rely on whether the new cases of diabetes involved subjects with preexisting glucose abnormalities. Dr. Quon similarly does not discuss whether cases of new onset diabetes involved patients with normal or abnormal baseline blood glucose levels. *See* Pfizer Ex. 42. Because Dr. Jewell's misuse of the term "glucose abnormalities" does not affect the causation opinions of Plaintiffs' experts who actually offer such opinions, it provides no basis to exclude any of those opinions.

Pfizer ignores, as well, that in his rebuttal report, Dr. Jewell separated the SPARCL study subjects with baseline glucose levels under 100 mg/dL from those with baseline glucose levels between 100 mg/dL and 126 mg/dL and thus differentiated between the cases of new-onset diabetes in study subjects without baseline glucose abnormalities and those the cases of new-onset diabetes in pre-diabetics. When he did so, he concluded that there is no statistical basis to claim that the elevated risk of new onset diabetes in SPARCL was limited to patients with pre-diabetes. Thus, his failure to separate these two groups in his initial report did not in any way obscure or mis-state the real risks of new onset diabetes across all subjects in the SPARCL trial.

3. Dr. Jewell's Analysis of the ASCOT Trial Is Reliable

Pfizer's attacks on Dr. Jewell's analysis of the ASCOT trial are the heart of its motion. Although Pfizer couches its critiques as general issues, the examples it uses for its claims of

"cherry-picking" and "manipulation" nearly all pertain to Dr. Jewell's analysis of the ASCOT study. *See* Pfizer Br. at 33-37. Separate and apart from the fact that Dr. Jewell's analysis of ASCOT formed no part of the causation opinions of Plaintiffs' experts, and is contained solely in Dr. Jewell's rebuttal report, Pfizer's criticisms provide no basis to exclude this portion of Dr. Jewell's analysis.

First, Pfizer claims that Dr. Jewell was "cherry-picking" data when he chose not to analyze the ASCOT trial the first time around. As discussed above, however, Dr. Jewell simply mirrored the selections of Pfizer's consultant, Dr. Waters; he did not make his own selection of studies, still less one designed to reach a preordained result. Moreover, Plaintiffs' other experts did not rely on Dr. Jewell's selections, and considered ASCOT through the meta-analyses that included it. In addition, Dr. Jewell ultimately *did* analyze the ASCOT trial, so that its omission from the original report is irrelevant to his ultimate conclusions. Moreover, when he did analyze ASCOT, it too showed a significantly increased risk of new-onset diabetes that was entirely consistent with the increased risk shown in the SPARCL trial.

Second, Pfizer claims that when Dr. Jewell analyzed the data from the ASCOT trial, he did it "wrong." In particular, Pfizer claims that Dr. Jewell "manipulated" the data because he did his own analysis of it, rather than relying on the analysis performed by Pfizer. *See* Pfizer Br. at 36-38. This is nonsense. There were good reasons for Dr. Jewell to perform the analysis he did and he is fully qualified to perform it.

First, the ASCOT protocol used a non-standard definition of diabetes, because it required that subjects have actual diabetes symptoms, rather than simply defining diabetes by blood glucose levels, as both the ADA and the World Health Organization ("WHO") do. *See* Pfizer Ex. 34 at 5. The ASCOT Endpoint Manual specified the WHO criteria, but "does not clearly state what criteria were used to determine whether or not an eligible patient met the diabetes endpoint." *Id.* Similarly, the published results of the ASCOT study report a statistically insignificant increase in the risk of diabetes in those taking Lipitor compared to placebo, but the article does not describe the criteria used to define diabetes.

Second, the ASCOT protocol specified that analyses would be performed "without adjusting for baseline factors," but that an "adjustment for important prognostic variables will be done as complementary analyses." Pfizer Ex. 34 at 6. The final ASCOT-LLA Statistical Analysis Plan specified that the analyses *would* be adjusted for baseline factors. Neither Pfizer's internal clinical study report nor the published results of the study included results from any analysis that adjusted for baseline characteristics. In 2010, however, Pfizer performed a re-analysis of the ASCOT-LLA data in response to an inquiry from the UK Medicines and Healthcare Products Regulatory Agency ("MHRA"), the British equivalent of the FDA, in which it did adjust for significant baseline factors. *Id.* at 7. But even then, Pfizer was not clear in how it was defining diabetes for purpose of the re-analysis; indeed, its re-analysis muddied the waters by describing what was done in the original report differently from both the original protocol *and* the Endpoint Manual. Thus, as Dr. Jewell concludes: "In sum, it is unclear how diabetes was defined in ASCOT-LLA and, by extension, Pfizer's 2010 letter to the MHRA." *Id.* at 8. In analyzing the ASCOT-LLA study, therefore, Dr. Jewell had little choice but to use the underlying data of blood glucose measurements to determine the number of study participants who developed new onset diabetes during the study.

But in doing so, Dr. Jewell neither manipulated the data nor used an unreliable methodology. Rather, he applied a standard ADA definition of diabetes, the one used in nearly all of the other studies, to the actual underlying data reported by the study authors to determine the number of cases of new onset diabetes properly defined. Pfizer's own expert, Dr. Wei, replicated this portion of Dr. Jewell's analysis and agreed with that Dr. Jewell correctly counted the number of cases. *See* Exhibit I at 105:13-106:6. Dr. Jewell then performed precisely the same kind of statistical calculations on the data that Dr. Waters performed in his analysis. *See* Pfizer Ex. 34 at 13. Pfizer's complaint thus comes down to the fact that Dr. Jewell counted the cases of new onset diabetes himself, using the blood glucose levels reported in the study, rather than relying on the count made by the authors of the published results. But since there was no way to tell what definition the authors of the published results had used, and therefore no way to

replicate their analysis, clearly it was *more* reliable, not less, for Dr. Jewell to do the count for himself, using the data Pfizer provided and standard diagnostic criteria. Dr. Jewell's analysis of the ASCOT-LLA data for himself would provide no basis to exclude his opinion about it (even if Pfizer had properly moved to exclude that opinion).

C. Dr. Abramson Does Not Purport to Offer an Opinion Concerning Causation

Pfizer sweeps Dr. John Abramson into its attack on Plaintiffs' causation opinions, but cannot identify a single portion of Dr. Abramson's Report that purports to opine that Lipitor causes diabetes. Dr. Abramson's report clearly lays out the twelve opinions he is offering. *See* Abramson Report at ¶¶ 11-22. These opinions compare what Pfizer's clinical trials and other trials it was aware of showed with what Pfizer said in its marketing about Lipitor. *Id.* Dr. Abramson describes various of the trials as showing an "association"; nowhere does he offer the opinion that Lipitor causes diabetes. (Of course, to the extent that Dr. Abramson's more detailed discussion of his opinions assumes that the association is in fact causal, he is entitled to rely on Dr. Singh for that finding.) Pfizer does not assert – nor could it – that any of the experts that *do* opine about causation rely on any portion of Dr. Abramson's opinion. Moreover, Dr. Abramson's report is the subject of an entirely separate motion focused on the opinions he *does* offer. To the extent that Pfizer's argument is that Dr. Abramson's opinions should be excluded because he relies on the causation opinions of Drs. Gale, Quon, Singh, and Roberts, that argument should be rejected because, as discussed above, those underlying opinions are fully admissible.

II. THE GENERAL CAUSATION TESTIMONY OF PLAINTIFFS' EXPERTS SHOULD NOT BE LIMITED BY DOSE OR RISK FACTORS

Pfizer argues that Plaintiffs' experts should be limited to an opinion they do not hold – that Lipitor only causes diabetes at doses of 80 mg or more. But there is no basis for this limitation.

Plaintiffs do not dispute that dose is important and do not contend that miniscule quantities of atorvastatin can cause diabetes. The issue is whether the threshold here is 80 mg per day, as Pfizer would have it, or 10 mg per day, Plaintiffs believe.

Pfizer contends there is no evidence that Lipitor can cause diabetes as dosages less than 80 mg per day, but this is not so. The placebo-controlled clinical trials that Pfizer submitted with its NDA were based on doses of 10 mg per day. As discussed above, those trials showed a threefold increased risk of clinically-significant elevations in blood glucose levels in study participants taking atorvastatin in comparison to placebo; the average elevation among those with these significant elevations was 30 mg/dL. The clinical trials alone provide a basis to believe that Lipitor affects glucose levels sufficient to cause diabetes even at doses of 10 mg. But those trials do not stand alone.

The ASCOT study, too, involved doses of 10 mg. Pfizer contends that this study showed no increased risk of diabetes, but, as discussed above, it is impossible to determine how Pfizer was defining diabetes when it made that determination. Using a standard ADA definition, and controlling for baseline predictors of new-onset diabetes, Dr. Jewell's analysis shows that ASCOT study participants taking Lipitor were at a statistically-significant increased risk of diabetes. Because this study, too, involved the 10 mg dose, it, too, supports Plaintiffs' position that Lipitor can cause diabetes at that dose.

Pfizer's experts read ASCOT differently, and they read the totality of the causation evidence differently as well. *See* Pfizer Br. at 42-43. But this is a dispute to be resolved by the jury. Plaintiffs' evidence of causation at the 10 mg dose is based on scientifically sound studies and ought not be excluded.

Pfizer also contends that Plaintiffs' causation opinions should be limited to patients with three or more of four risk factors specified by Pfizer. Pfizer bases this view on a single analysis of three studies, one of which (IDEAL) compared Lipitor to another statin, rather than a placebo and another of which (TNT) compared different doses of Lipitor. *See* Pfizer Br. at 45, *citing* Waters (2011). This analysis – which was performed by a Pfizer consultant and three Pfizer

employees -- does not support Pfizer's position: It demonstrates a significantly elevated risk of diabetes with Lipitor in SPARCL patients when controlled for all four baseline risk factors.

Pfizer's own expert does not even adopt Pfizer's position. Pfizer's expert argues that the SPARCL data demonstrate a significantly increased risk of diabetes in patients with *two* or more baseline risk factors. Wei Report at 38 ¶ 132. Although Pfizer's expert in this case adopts this position, Dr. Jewell's rebuttal report shows, that this expert's conclusion was based on application of a double-standard to one of the statistical tests used in the analysis. *See* Pfizer Ex. 34 at 30. Moreover, when Dr. Jewell himself performed an analysis similar to the Waters analysis, he found, as Waters et al. found, that the four predictors Dr. Waters identified "do not explain the significantly increased risk of NOD associated with atorvastatin treatment." *Id.* at 32. He further demonstrated, through a stratified analysis of the SPARCL trial, that the increased risk was not limited to patients with pre-diabetes. *Id.* at 34.

Significantly, Pfizer finds no fault with this portion of Dr. Jewell's analysis. It seeks to exclude this conclusion without even mentioning Dr. Jewell or attempting to find flaws in his methodology or his conclusion (other than to say that Dr. Waters found something different).

CONCLUSION

For the foregoing reasons, this Court should deny in its entirety Pfizer's motion to exclude Plaintiffs' expert testimony that Lipitor can cause diabetes and/or to limit that testimony.

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APPENDIX I: META-ANALYSES

Rajapathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. *Statin therapy and risk of developing type 2 diabetes: a meta-analysis.* DIABETES CARE. 2009;32:1924.	A summary meta-analysis of clinical trials using data from, among others, WOSCOPS, ASCOT JUPITER and CORONA. These included 57,593 patients with a mean follow-up of 3.9 years. The results showed a statistically significantly increased risk of type 2 diabetes without evidence of heterogeneity across trials.
Sattar N, Preiss D, Murray HM, *et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials.* LANCET. 2010;375:735-42*l*.	A collaborative meta-analysis of 13 trials of statins with 91,140 participants. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity between trials 02=11 %). The studies included used varying criteria for the diagnosis of diabetes.
Mills EJ, Wu P, Chong G, Ghement I, Singh S, Aki EA, Eyawo 0, Guyatt G, Berwanger 0, Briel M. *Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials.* QJM. 2011 ;104:109-24	A summary meta-analysis of statin trials. Among 17 randomized controlled trials that involved 111,002 participants, statin therapy suggested an increased risk of diabetes, 2,215(3.8%) in statins vs. 2,048 (3.5%) in control.
Naci H, Brugts J, Ades T. *Comparative tolerability and harms of individual statins: a study-level network meta-analysis of246 955 participants from 135 randomized, controlled trials.* CIRC CARDIOVASC QUAL OUTCOMES. 2013 ;6:390-9.	A pairwise and network meta-analysis of statins including a total of 246,955 participants. According to pairwise meta-analyses, statins as a class resulted in significantly higher odds of diabetes mellitus.
Coleman CI, Reinhart K, Kluger J, White CM. *The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis ofrandomized controlled trials.* CURR MED RES OPIN. 2008;24:1359-62.	A systematic review and meta-analysis to determine whether statins reduced the risk of diabetes. They included only 5 trials with 39,791 participants. Although Coleman found that, looking at all statins combined, there was no significant alteration in the participants' risk of diabetes, after excluding pravastatin, they reported a significant increase in the risk of diabetes from the other statins.
Preiss D, Seshasai SR, Welsh P, Murphy SA, *et al. Risk of incident diabetes with intensive-dose compared with moderatedose statin therapy: a meta-analysis.* JAMA.2011 ;305(24):2556-64	A meta-analysis comparing intensive dose statin therapy (atorvastatin 80 mg, simvastatin 40 and 80 mg) to moderate dose statin therapy (simvastatin 20 mg or pravastatin 40 mg or atorvastatin 10 mg). 13 Five trials with 32,752 participants were selected. Among 16,408 patients randomized to intensive dose statins, 1,449 in developed diabetes (8.8%), compared to 1,300 out of 16,344 in the moderate dose group (8.0 %). Intensive dose statin was associated with an approximate 12% increased risk of type 2 diabetes compared to moderate dose statins for new-onset diabetes.
Navarese EP, Buffon A, Andreotti F, *et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus.* AM J CARDIOL. 2013 ;111:1123-30.	A network meta-analysis to evaluate the risk of diabetes with various types of statins and evaluate dose effects, including 17 trials with 113,394 participants. Results showed that pravastatin 40 mg had the lowest risk of diabetes when compared to placebo, while rosuvastatin 20 mg had the highest risk of diabetes. Atorvastatin had an intermediate risk of type 2 diabetes compared to placebo.

Waters DD, Ho JE, Boekholdt SM, DeMicco DA, Kastelein JJ, Messig M, Breazna A, Pedersen TR. *Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes*. J AM COLL CARDIOL. 2013 ;61(2):148-52.	Analysis of three atorvastatin-specific trials that also reported on the risk of diabetes, TNT, IDEAL, and SPARCL, using, for the latter, WOSCOPS diabetes criteria, instead of ADA criteria, nonetheless showing in that trial a statistically significant increased risk of type 2 diabetes with 80 mg of atorvastatin compared to placebo.
Goodarzi MO, Li X, Krauss RM, Rotter Il, Chen YD. *Relationship of sex to diabetes risk in statin trials*. DIABETES CARE. 2013 ;36:e100-1.	A meta-regression using data from 13 placebo-controlled statin trials to examine the effect of sex on diabetes. Reported a significant association between the proportion of women in statin trials and the odds ratio of diabetes: as the proportion of women increased the odds ratio of diabetes also increased.
Cai, R., Yuan, Y., Zhou, Y., Xia, W., Wang, P., Sun, H., Wang, S. (2014). *Lower intensified target LDL-c level of statin therapy results in a higher risk of incident diabetes: A meta-analysis*. PLoS ONE 9(8): e104922. doi:10.1371/joumal.pone.0104922	A meta-analysis of statin trials to determine whether statin therapy with lower LDL-C target levels contributes to a higher risk of new-onset diabetes. in analyzing 14 trials with 95,102 non-diabetic participants that the odds ratio was increased to 1.33 when the target LDL-C was less than or equal to 1.8 mmol/L and 1.16 when the target LDL-C was between 1.8 and 2.59 mmol/L. Meta-regression analyses ·were performed and these revealed that in addition to target LDL-C level, female sex, age, baseline total cholesterol, and relative LDL-C reduction were risk factors for new-onset diabetes resulting from statin therapy

APPENDIX II: OBSERVATIONAL STUDIES

Culver AL, Ockene IS, Balasubramanian R, *et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative*. ARCH INTERN MED. 2012; 172:144-52.	A retrospective analysis of the Women's Health Initiative (WHI) in the US that showed that statin use was associated with a 71 % increased risk of incident diabetes among post-menopausal women; after adjustment for potential confounders, the hazard ratio (HR) was significant at 1.48. The specific adjusted estimates for atorvastatin were noted to be HR 1.61. (Exhibit __)
Chen C-W, Chen T-C, Huang K-Y, Chou P, Chen P-F, *et al. Differential Impact of Statin on New-Onset Diabetes in Different Age Groups: A Population-Based Case-Control Study in Women from an Asian Country*. PLoS ONE. 2013. 8(8): e71817.	An evaluation of the association between statins and diabetes in females using a case-control study design in the Taiwanese National Health Insurance Database. Statin-exposure was statistically significantly associated with increased new-onset diabetes risks using multivariate analysis, with an OR of 2.80 for atorvastatin. Dose response association was observed in the case of atorvastatin providing further evidence of a causal association.
Ma T, Tien L, Fang CL, Liou YS, Jong GP. *Statins and new-onset diabetes: a retrospective longitudinal cohort study*. CLIN THER 2012; 34: 1977-83.	An evaluation of the effect of statins on diabetes among patients with dyslipidemia and hypertension also in Taiwan. The risk of new onset diabetes after adjusting for sex and age was higher among users of pravastatin and atorvastatin than among nonusers; also demonstrated that atorvastatin had a dose-response effect.
Wang KL, Liu CJ, Chao TF, *et al. Statins, risk of diabetes, and implications on outcomes in the general population.* J AM COLL CARDIOL. 2012;60(14):1231-8.	Also from Taiwan National Health Insurance Beneficiaries, this study followed participants for a mean of 7.2 years to evaluate their risk of diabetes in the general population. Statin use significantly increased the hazards of diabetes occurrence.
Danaei G, Garcia Rodriguez LA, Fernandez Cantero O, Heman MA. *Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival*. DIABETES CARE. 2013; 36:1236-40.	Using data from the General Practice Research Database in the UK, the team showed that statin initiation was associated with a 14% increased risk of diabetes in a cohort study.
Izzo R, de Simone G, Trimarco V, Giudice R, *et al. Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk*. NUTR METAB CARDIOVASC DIS. 2013; 23:1101-	Evaluated the incidence of diabetes among patients with hypertension without CVD and diabetes at baseline in Italy; followed up patients for at least a year. At the end of follow-up period, statin users were more likely to have prevalent diabetes (18.1 % vs 7 .2%; P< 0.0001), but no statistically significant difference in incident diabetes (10.2 % vs 8%).
Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. *Risk of incident diabetes among patients treated with statins: population based study*. BMJ. 2013 May 23;346:f2610.	A population-based study among elderly residents in Ontario, Canada examining the risk of incident diabetes among new-users of statins comparing the more potent statins (atorvastatin) to the less potent statins (pravastatin). Atorvastatin was associated with a significantly increased risk of diabetes compared to pravastatin.

Dormuth Colin R, Filion Kristian B, Paterson J Michael. *et al. Higher potency statins and the risk of new diabetes: multicenter observational study of administrative databases.* BMJ 2014: 348 :g3244.	Compared higher potency statins (rosuvastatin 10 mg, atorvastatin 20 mg and simvastatin 40 mg) with lower potency statins using a nested case-control design. Use of higher potency statins after a major cardiovascular event or procedure was associated with significant increase in the risk of new onset diabetes (NOD) compared with lower potency statins in Western populations (US, Canada and UK); risk increase appeared be highest in the first four months of use.
Corrao G, Ibrahim B, Nicotra F, *et al. Statins and the Risk of Diabetes. Evidence From a Large Population-Based Cohort Study.* DIABETES CARE. 2014 Jun 26. [Epub ahead of print].	Evaluated the link between adherence to statin therapy and the risk of developing diabetes in an Italian cohort. Even after controlling for an unknown confounder (obesity), which increased the risk of diabetes threefold and was prevalent at 37%, the study found a link between statins and diabetes.
van de Woestijne AP, van der Graaf Y, Westerink J, Nathoe HM, Visseren FL. *Effect of Statin Therapy on Incident Type 2 Diabetes Mellitus in Patients With Clinically Manifest Vascular Disease.* AM J CARDIOL. 2014 Nov 29. pii: 50002-9149(14)02162-6. doi: 10.1016/j.amjcard.2014.11.021. [Epub ahead of print].	A prospective cohort study among participants in the Second Manifestation of Arterial Disease (SMART) cohort. There were 4,645 patients with established vascular disease without diabetes at baseline. Statin therapy was associated with an increased risk of incident type 2 diabetes when adjusted for age, gender, body mass index, plasma high-density lipoprotein cholesterol, and plasma triglyceride levels. The increase in risk was regardless of the number of metabolic syndrome characteristics and pronounced in patients with low baseline glucose levels.
Macedo AF, Douglas I, Smeeth L, Forbes H, and Ebrahim S. *Statins and the risk of type 2 diabetes mellitus: cohort study using the UK clinical practice pesearch datalink.* BMC CARDIOVASCULAR DISORDERS. 2014; 14(85	Using UK Clinical Practice Research Datalink over 20 years, compared rates of T2DM between statin users and non-users. The study cohort comprised of 2,016,094 individuals (statin, n=430,890, non-statin controls, n=l,585,204) with a mean follow-up time of 5.43 years for statin users and 3.89 years for nonusers. 11,734 were new Atorvastatin users comprising approximately 26% of the statin users. During follow-up, 130,395 individuals developed T2DM. Statin use was associated with an increased risk of T2DM (HR 1.57; 95% CI 1.54-1.59.